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CURRENT CANCER RESEARCH

I. CARCINOGENESIS AND RELATED BIOLOGY

A. BLADDER

1. INDUCTION BY CHEMICALS

1. DEVELOPMENT OF AN IN VITRO ORGAN CULTURE SYSTEM FOR BLADDER CARCINOGENESIS

Norman, J. T., Hodges, G. M., Spacey, G., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

In an attempt to reduce the number of variables inherent in in vivo carcinogenesis systems and for studies on epithelial-stromal interaction in the neoplastic process, an in vitro organ culture system is being developed based on the in vivo N-methylnitrosourea (MNU)-bladder model. Bladder organ culture treatment protocols are being investigated with particular attention to conditions optimal for both carcinogenic effect and tissue maintenance.

Treatment of the explants with the equivalent of an in vivo single initiating but non-tumorigenic dose of MNU produces a hyperplastic response of the urothelium which is retained over a culture period of at least four weeks; a cell surface patterning of microvilli is observed similar to that seen in the in vivo treated tissue. Experiments are in progress to establish an in vitro urothelial response to MNU at in vivo tumorigenic dose levels.

2. FURTHER INVESTIGATIONS WITH A 2-STAGE MODEL DESIGNED TO DETECT LOW POTENCY BLADDER CARCINOGENS AND CO-CARCINOGENS

Hicks, R. M., Severs, N., Chowaniec, J., University of London, Middlesex Hospital Medical School, School of Pathology, Dept. of Cell Pathology, *Cleveland St., London W1P 7LD, England, United Kingdom*

OBJECTIVE: To further develop our rabbit bladder model for detecting weak bladder carcinogens and co-carcinogens and to investigate the biological prinicples underlying multistage carcinogenesis, initiation and promotion.

APPROACH: We have developed a rat model which employs the principle of 2-stage carcinogenesis, to test compounds with suspected carcinogenic or co-carcinogenic potential for the bladder. The urothelium is exposed to a low dose of a known bladder carcinogen, and the test compound then administered to the animal by an appropriate route. If the test compound is also organotropic for the bladder and is either a solitary carcinogen, co-carcinogen or a promoter, it will increase the yield of tumors obtained with the low dose of the initiating carcinogen on its own. The model is also being used to investigate the dose response of the urothelium to a) the initiator and b) some of the test compounds; to determine the duration of the initiating effect; to compare the effect of single and 'split' doses of the same carcinogen; to identify useful and reliable initiators of carcinogenesis in the urothelium; and to study in depth the subcellular changes associated with the early, clinically 'silent' stages of neoplastic growth in the urothelium.

PROGRESS: N-methyl-N-nitrosourea (MNU) was used as the initiating carcinogen for a series of experiments. Saccharin and cyclamate both greatly increase the yield of bladder cancers in the MNU-initiated bladder and we conclude these compounds are weak initiators but powerful promoters of carcinogenesis in the rat bladder. 2-naphthylamine was both synergistic with MNU and also a solitary carcinogen producing an incidence of approximately 25 percent bladder cancer when tested at high doses on its own. Coffee and caffeine did not significantly increase the tumor yield after initiation with MNU.

3. BIOCHEMICAL MECHANISMS IN EXPERIMENTAL BLADDER CANCER

Irving, C. C., Daniel, D. S., Wright, R. K., Roszell, J. A., Murphy, W. M., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Urology, *62 S. Dunlap St., Memphis, Tennessee,* 38103, United States of America

The main objective of these studies is to learn more about the mechanisms by which known bladder carcinogens induce urinary bladder cancer in experimental animals. The model system that has been selected for study in this project is the induction of bladder cancer in rats with N-butyl-N-(4-hydroxybutyl)nitrosamine (BHBN) and its principal urinary metabolite, N-butyl-N-(3-carboxypropyl) nitrosamine (BCPN). The urinary bladder is the only organ in the rat in which cancer is induced by the administration of BHBN or BCPN, and the incidence of bladder cancer in exposed rats is 100%. More than 90% of these bladder cancers are transitional cell carcinomas.

The research proposed in this application is directed towards learning what metabolite of BHBN or BCPN is involved in the induction of bladder cancer, i.e., how are these nitrosamines metabolically activated? The hypothesis being tested is that a stable precursor of an activated metabolite derived from BCPN is formed in the liver and is excreted in urine, where it undergoes hydrolysis (either intravesically or intracellularly after absorption) with the liberation of an activated metabolite. At the present time, we do not believe that BCPN itself is metabolically activated directly by rat bladder epithelial cells.

4. DNA REPAIR IN CARCINOGENESIS

Cox, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee,* 38104, United States of America

The proposed research has been concerned with the interaction of chemical carcinogens with DNA and the consequences (damage and repair) of this reaction as it relates to the integrity of the cell. We have used mainly alkylating carcinogens that induce cancer in various tissues of the rat, depending upon the route of administration and dose. Data from the study of methylnitrosourea induced rat bladder and mammary gland cancer support the hypothesis that O6-methylguanine plays a vital role in the initiation of tumors in these organs. Methylnitrosourea was also demonstrated in the rat brain to bind specifically to DNA that was digested by DNAse I in whole nuclei. In this same system O6-methylguanine was shown to be more stable in the resistant regions of chromatin. These studies are continuing with a liver system where a single dose of the carcinogen is sufficient for the induction of cancer.

5. CYTOCHEMICAL PROBES OF UROTHELIAL TUMOR CELLS

Vanderlaan, M., Mendelsohn, M. L., Jensen, R. H., King, E. B., Walton, J., University of California, Central Office, Lawrence Livermore Lab., Biomedical Sciences Division, *P.O. Box 808, Livermore, California,* 94550, United States of America

We are applying quantitative cytochemical methods to the study of bladder tumor development in Fisher rats fed N-butyl-N-(4-hydroxybutyl)-nitrosamine. This study will further understanding of the basic biological steps in bladder tumor progression and may provide a cytochemical foundation for improvements in exfoliated cell diagnostic cytology. Our attention is focused on characterizing the early cellular changes in tumors. The temporal acquisition of cytochemical changes is being related to carcinogen protocol, bladder pathology, conventional diagnostic cytology, and electron microscopic observations. Quan-

titative cytochemical measurements of cell size, DNA content, protein content, and protease, esterase, and dehydrogenase activities are being made. Measurements of fluorescence and absorbtion are made using static cytometers and flow fluorocytometers as appropriate.

6. IN VIVO BLADDER CARCINOGENESIS OF NITROSOAMINES

Oyasu, R., Miyata, Y., Izumi, K., Northwestern University, Chicago Campus, School of Medicine, Dept. of Pathology, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

The immediate objective of the proposed investigation is to ascertain whether urine contains a factor(s) which serves as a promoting agent(s) in urinary bladder neoplasia. Our studies are based on the hypothesis that urine may contain minute amounts of carcinogen(s) derived from either exogenous or endogenous sources and that these induce cancer only when they are present in sufficiently high concentration or act in concert with a second substance in urine which may serve as a co-carcinogen or as a promoter.

Available evidence indicates that the urine contains a number of substances which are known to stimulate cell growth, and it is conceivable that some of them may play the role of either tumor promoter or co-carcinogen. The proposed investigation is intended 1) to study the role of urine, specifically its possible role as a co-carcinogen and/or a promoter - as a study model, heterotopically transplanted bladders (HTB) of rats diverted from urine flow will be used; 2) to study the role of urinary constituents as possible co-carcinogens and/or promoters - the substances to be tested will be epidermal growth factor and polyamines; and 3) to test suspected proximate carcinogens using HTBs as a model.

7. STUDIES ON EXPERIMENTAL BLADDER TUMORS

Cohen, S. M., Friedell, G. H., Jacobs, J. B., Murasaki, G., St. Vincent Hospital, Dept. of Pathology, *25 Winthrop St., Worcester, Massachusetts,* 01604, United States of America

A reliable, highly reproducible model of bladder cancer in male Fischer rats using N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide (FANFT) has been developed. The natural history of experimental bladder cancer, patterns of invasion, dose response, and the reversibility or irreversibility of early lesions have been determined. Light, histochemical, scanning (SEM), transmission, freeze fracture, and quantitative electron microscopy of the various lesions during the course of bladder carcinogenesis were evaluated with emphasis on SEM evaluation of surface features. SEM evaluation of urinary cytology in the rat model and in humans has been developed. The presence of initiation and promotion in bladder carcinogenesis was evaluated using 0.2% FANFT for 6 weeks as initiator and either sodium saccharin or DL-Tryptophan as promoter. Both promoters significantly increased the incidence of bladder cancer in this model, but neither induced bladder tumors when fed without first feeding FANFT. Repeating this experiment but using 4 weeks of FANFT for initiation and sodium saccharin or L-Tryptophan, rather than DL-tryptophan as promoters again gave significant incidences of bladder tumors. Mild hyperplasia, but no tumors, was induced by sodium saccharin fed without FANFT prefeeding, and the effect showed a dose response. Additional studies are underway evaluating the properties of the stages of bladder carcinogenesis.

BIBLIOGRAPHIC REFERENCES: Fukushima, S., and Cohen, S.M. Saccharin-induced hyperplasia of the rat urinary bladder. Cancer Res., 40:734-736, 1980. Koo, C.H., Pauli, B.U., Cohen, S.M., and Weinstein, R.S. Angiogenesis during early stages of chamical carcinogenesis of rat bladder epithelium. Fed. Proc., 39:641, 1980.

8. RENAL MEDULLARY METABOLISM OF CHEMICAL CARCINOGENS - A NEW HYPOTHESIS FOR THE GENESIS OF URINARY BLADDER CANCER

Zenser, T. V., St. Louis University, School of Medicine, Dept. of Biochemistry, *1402 S. Grand Blvd., St. Louis, Missouri,* 63104, United States of America

The objectives of this research proposal will be: 1) investigation of the mechanism of N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) and 2-amino-4-(5-nitro-2-furyl)thiazole (ANFT) cooxidative metabolism by prostaglandin endoperoxide synthetase; 2) determination of the presence of reactive intermediate formed during FANFT and ANFT cooxidative metabolism; 3) identification of products of FANFT and ANFT cooxidative metabolism; and 4) determination of the distribution of renal FANFT deformylase activity.

Cooxidative metabolism will be defined as metabolism which is initiated by specific substrates and blocked by specific inhibitors of prostaglandin endoperoxide synthetase. Renal inner medullary microsomes and slices will be used to characterize cooxidative metabolism. Metabolic requirements will be used to determine whether the fatty cyclooxygenase or prostaglandin hydroperoxidase activities of prostaglandin endoperoxide synthetase are involved in cooxidation. Radiolabeled FANFT and ANFT will be synthesized and used to determine the presence of reactive intermediates during cooxidative metabolism. Metabolites will be purified by gas liquid and high pressure liquid chromatographic techniques and identified by gas chromatograph mass spectral analysis. Identification of metabolites will allow determination of the reactive intermediate(s)'s structure. These intermediates may be the ultimate carcinogens in the induction of bladder cancer. The deformylation of FANFT will be analyzed by gas liquid chromatographic techniques. This proposal will provide further insight into the genesis of chemically-induced urinary bladder cancer and a more rational approach to its prevention. It should be noted that if prostaglandin endoperoxide synthetase is involved in the genesis of chemically-induced bladder cancer, certain non-steroidal anti-inflammatory agents and antioxidants inhibit the activity of this enzyme.

9. BLADDER CANCER - METABOLISM OF CARCINOGENS AND PREVENTION

Zenser, T. V., St. Louis University, School of Medicine, Dept. of Biochemistry, *1402 S. Grand Blvd., St. Louis, Missouri,* 63104, United States of America

The objectives of this research proposal will be: a) identification of products of N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) and 2-amino-4-(5-nitro-2-furyl)-thiazole (ANFT) cooxidative metabolism; b) investigation of the mechanism of FANFT and ANFT cooxidative metabolism by prostaglandin endoperoxide synthetase (PES); c) determination of reactive intermediates formed during FANFT and ANFT cooxidative metabolism; d) determination of the distribution of renal FANFT deformylase activity; and e) determination of the in vivo effects of PES-mediated cooxidation on the incidence of chemically-induced urinary bladder cancer using feeding studies.

Cooxidative metabolism will be defined as metabolism which is initiated by specific substrates and blocked by specific inhibitors of PES. Renal inner medullary microsomes and slices will be used to characterize cooxidative metabolism. Metabolites will be purified by gas liquid and high pressure liquid chromatographic techniques and identified by gas chromatograph mass spectral analysis. Metabolic requirements will be used to determine whether the fatty cyclooxygenase or prostaglandin hydroperoxidase activities of PES are involved in cooxidation. Radiolabeled FANFT and ANFT will be synthesized.

The effect of aspirin or indomethacin, specific inhibitors of cooxidative metabolism, on the incidence of FANFT-induced bladder cancer will be examined. Urinary cooxidative metabolites of FANFT and ANFT will be identified. Urinary prostaglandin E2 will be analyzed by a specific radioimmunoassay technique. This proposal will provide further insight into the genesis of chemically-induced urinary bladder cancer and a more rational approach to its prevention.

10. AROMATIC AMINE N-OXIDATION IN BLADDER CANCER

Brill, E., University of Miami, School of Medicine, Dept. of Pharmacology, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida,* 33152, United States of America

The objective of this research is to establish whether the unconjugated N-arylhydroxylamine and/or the nitroso derivatives of the bladder carcinogens naphthylamine, 4-biphenylamine and 2-fluorenylamine, function as the proximal urinary and ultimate cellular carcinogens that induce tumor formation in the urinary bladder epithelium of the dog. Experimental evidence indicates that these N-oxidized metabolites interact with the DNA of the target tissue. Studies will be conducted to determine the nature and extent of these reactions with the DNA of the bladder epithelium and the possible role of the resulting

modifications in the mechanism of the irreversible initiation to eventual malignancy of the target cells.

We are engaged in the development of immunochemical methods that will have the necessary sensitivity and specificity for the study of these nucleic acid modifications induced in vivo in the urinary bladder epithelium by the exposure to the carcinogenic aromatic amines and their metabolic N-oxidation products. The metabolic activity of the bladder mucosa and its possible role in DNA-carcinogen interaction is under investigation.

11. CONJUGATION REACTIONS IN ARYLAMINE CARCINOGENESIS

Irving, C. C., Daniel, D. S., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Urology, *62 S. Dunlap St., Memphis, Tennessee,* 38103, United States of America

The overall objective of this project is to study biochemical mechanisms involved in the metabolic activation of arylamines in non-hepatic target organs, with major emphasis on the urinary bladder. Recent studies from other laboratories have suggested a role for the N-glucuronide conjugates of the N-arylhydroxylamine metabolites in the induction of bladder cancer in susceptible species. The synthesis of a number of N-glucuronide conjugates will be undertaken for metabolic studies in appropriate host animals. If sufficiently stable, these N-glucuronides will be tested for carcinogenicity and for their ability to transform bladder epithelial cells in vitro. The project will also be concerned with determination of the potential role of N-sulfonate conjugates of N-arylhydroxylamines in bladder cancer induction. It is possible that N-glucuronides and N-sulfonates of N-arylhydroxylamines are involved in the induction of other cancers by arylamines in experimental animals.

BIBLIOGRAPHIC REFERENCES: C.C. Irving, R. Cox and W.M. Murphy. Influence of dose of N-methyl-N-nitrosourea on the induction of urinary bladder cancer in rats. Cancer Letters, 8, 3-7 (1979). M. Mochizuki, C.C. Irving, T. Anjo, Y. Wakabayashi, E. Suzuki and M. Okada. Synthesis and mutagenicity, 4-(N-butylnitrosamino)-4-hydroxybutyric acid lactone, of a possible activated metabolite of the proximate bladder carcinogen, N-butyl-N-(3-carboxypropyl)nitrosamine. Cancer Res., 40, 162-165 (1980).

12. THE ROLE OF N-HYDROXY ARYLAMINE IN BLADDER CARCINOGENESIS

Kadlubar, F. F., Casciano, D. A., Flammang, T. J., Sofer, S., Matthews, A., Oglesby, L., U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., National Center for Toxicological Research, Division of Molecular Biology, *Jefferson, Arkansas,* 72079, United States of America

OBJECTIVES: Study the reactivity of the N-hydroxyarylamines and their glucuronide metabolites with nucleic acids and proteins; examine the role of the bladder epithelial cell in the metabolic activation of arylamines, N-hydroxyarylamines and nitroso- and nitroamines; study the metabolic N-oxidation of the arylamine bladder carcinogens by dog and human liver microsomes.

TEST COMPOUNDS: 1-naphthylamine, 2-naphthylamine; 4-aminobiphenyl, benzidine.

TEST ORGANISM AND ROUTE OF ADMINISTRATION: Rodent, rat, subcutaneous; dog and human liver microsomes - in vitro exposure.

DURATION OF EXPOSURE: Single exposures.

TEST PARAMETERS: Biochemistry, radiochmistry.

13. CARCINOGENICITY OF AROMATIC AMINES - AZO DYES

Lewis, T., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Biomedical & Behavioral Science, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

The purpose of this project is to compare and contrast the carcinogenic potential of two aromatic-azo dyes - disperse yellow 3 and acid black 52 - using the intratracheal and feeding routes of administration. Epidemiologic studies have revealed increases in the incidence of bladder tumors in workers exposed to aromatic-azo dyes above those of the general population and this study will investigate these epidemiological findings using laboratory rats and hamsters.

NCI is currently investigating or planning to study the carcinogenicity of 3 benzidine azo dyes of commercial significance -direct black 38, direct blue 36, and direct blue 218 - as well as certain other azo dyes in feeding studies. The two dyes selected in this study represent chemical structures whose carcinogenic activity is difficult to predict when inhalation and dermal are the primary routes of exposure, rather than the oral route. Bladder implants of disperse yellow 3 and oil orange SS, a compound having a chemical moiety similar to one found in acid black 52, have produced carcinomas of the bladder.

The population at risk from exposure to disperse yellow 3 and acid black 52, respectively, includes 3929 and 1207 workers in the dye industry. Production figures from the U.S. Tariff Commission indicate that 1,161,000 pounds and 762,000 pounds of disperse yellow 3 and acid black 52, respectively, were produced in the United States in 1976. This study is being conducted by contract (210-78-0032). Acute and subchronic range-finding studies have been completed. Chronic (18-month) administration of dyes is scheduled to begin in the first quarter of FY 80.

14. THE CARCINOGENICITY FOR TRANSITIONAL EPITHELIUM OF METABOLITES OF PHENACETIN

Stewart, J. H., Kanematsu Memorial Inst., Dept. of Medical Research, *Macquarie St., Sydney, N.S.W. 2000, Australia*

OBJECTIVE: It is the aim of this project to demonstrate which, if any, metabolites of phenacetin are carcinogenic for transitional epithelium.

APPROACH: Analgesics and their metabolites have been obtained in pure form commercially, or from Dr. Ian Calder, Department of Chemistry, University of Melbourne. Each has been incorporated with cholesterol in a ratio of 4:1, into 12mg pellets which are being implanted into the bladders of 16-18 week old CBA-H mice in batches numbering at least 40. The mice are being sacrificed 40 weeks after implantation of the pellets, and examined for tumor formation locally (by hand lens and histologically) and elsewhere in the body (by autopsy).

PROGRESS: Pellets containing cholesterol alone, hydroquinone, 1,2,5,6-dibenzanthracene, 4-amino-antipyrene, N-hydroxy-4-acetamidobiphenyl, acetyl salicyclic acid, paracetamol, phenacetin, N-hydroxy-phenacetin, 2-hydroxy-phenetidine, 2-hydroxy-p-acetophenetidine and 4, 4-diethoxy-azoxybenzene have been introduced into mice bladders. In addition, these and other chemicals have been tested for mutagenicity by Dr. Robert Baker of the School of Public Health and Tropical Medicine, University of Sydney. Only 1,2,5,6-dibenzanthracene and N-hydroxy-phenacetin are mutagenic, and these only after activation by liver homogenate.

15. METABOLISM AND BIOLOGICAL EFFECTS OF 4-ETHYLSULFONYLNAPHTHALENE-1 SULFONAMIDE (ENS)

West, R. W., Jackson, C. D., U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., National Center for Toxicological Research, Division of Carcinogenic Research, *Jefferson, Arkansas,* 72079, United States of America

OBJECTIVES: 1. Investigate relationships between biochemical factors (metabolism, pharmacokinetics, binding) and the occurrence of physical factors (urinary pH changes, crystalluria, and calculi). 2. Determine the casual relationship between these physical factors and the induction of bladder cancer in experimental animals. TEST COMPOUND: 4-Ethylsulfonylnaphthalene-1-sulfonamide. TEST ORGANISM: Rodent, BALB/c female mouse. ROUTE OF ADMINISTRATION: Interperitoneal injection or intubation. DURATION OF ADMINISTRATION: Single dose. EVALUATION PARAMETERS: Histopathology, metabolism studies (tissues and urine).

16. INTERACTIONS OF DIET/NUTRITION AND THE USE OF GENETICALLY DISTINCT ANIMAL STRAINS IN CARCINOGENESIS STUDIES

Littlefield, N. A., U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., National Center for Toxicological Research, *Jefferson, Arkansas,* 72079, United States of America

OBJECTIVES: To compare the influence of a natural ingredient diet and a semi-purified diet on the incidence of

'spontaneous' pathological observations, estrogen-induced lesions, and on liver and bladder carcinogenic lesions induced by 2-acetylaminofluorene (2-AAF) in both inbred and hybrid mouse strains.

MAJOR FINDINGS: The protocols are nearing finalization and plans are being formed to commence these studies in the near future. The short-term studies will start this summer.

Significance to Biomedical Research and the Program of the Institute: The primary significance of this experiment will be to contribute toward a data base comparing the responsiveness of mice to chemical insult when maintained on a semipurified diet vs. a cereal-base diet. Development of this data base is important since the semipurified diet is being evaluated for use in extensive diet and cancer studies. The use of standard diet for carcinogenesis bioassays will allow more valid comparisons between different assays by minimizing the variability in data due to diets.

17. ENVIRONMENTAL BLADDER CARCINOGENS

Radomski, J. L., Poupko, J. M., Hearn, W. L., Brill, E., University of Miami, School of Medicine, Dept. of Pharmacology, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida*, 33152, United States of America

The main objective of the project is to search for unrecognized bladder carcinogens in the human environment. Drugs, food additives, and industrial compounds are being considered. The metabolism of suspect chemicals will be examined in urine to determine whether carcinogenic N-hydroxy metabolites are formed.

Gas chromatography utilizing the electron capture detector, HPLC and GC-mass spectrometry will be the primary analytical methods used. Compounds being studied include caffeine, theobromine, theophylline, sulfadiazine, p-aminosalicylic acid, ampicillin, phenacetin, acetaminophen and acetanilid. Industrial amines being evaluated in dogs are methylenedianiline, 4,4'-methylene-bis(2-chloroaniline) dichlorobenzidine, 2,2-bis(p-amino-phenyl) propane and 4,4'-methylene-bis-('2-methylaniline). The N-hydroxy and nitroso derivatives of these amines are being synthesized.

Previous results show that dimethylnitrosamine is formed in the bladder during urinary tract infection. If DMN is an etiological factor in bladder cancer, it must be shown that it can be activated by and react with bladder mucosa. Examination of bladder mucosa has shown the presence of cytochrome P-450 which is capable of type II binding. These microsomes are capable of N-hydroxylating 4-aminobiphenyl. Possible activation of DMN is still under investigation.

Experiments to demonstrate the importance of the induction of hyperplasia by the naphthylamines and the inhibitions of this effect by retinoic acid will be carried out. The anticarcinogenic effect of 1-naphthylamine against 2-naphthylamine will be investigated.

BIBLIOGRAPHIC REFERENCES: The Primary Aromatic Amines: Biological Properties and Structure-Activity Relationships. Jack L. Radomski. Ann. Rev. Pharmacol. and Toxicol. (1979). Annual Reviews, Inc., Palo Alto, Calif., 129-158. Acid Catalyzed Rearrangements of the Glucuronic Acid Conjugate of 1-Naphthylhydroxylamine. Wm. Lee Hearn and Jack L. Radomski. J. Nat. Cancer Inst. (1980), in press.

2. MECHANISMS AND OTHER ASPECTS OF CARCINOGENESIS

18. NEGATIVE PI-MESON LARGE ANIMAL RADIOBIOLOGY - PHASE II

Douglas, B. G., British Columbia Cancer Research Centre, Medical Biophysics Unit, *601 W. 10th Ave., Vancouver, British Columbia*, V5Z 1L3, Canada

OBJECTIVE: This series of studies was designed to compare radiation effects on the skin and connective tissue of the bladder wall using the pig as an experimental animal. For both tissues this will involve measuring the effect of variation in fraction number on the total dose required to obtain a constant amount of radiation damage using conventional and negative pi-meson irradiations.

APPROACH: These experiments involve the use of arbitrary scales to evaluate skin damage and urinary bladder damage following single dose and fractionated photon and negative pi-meson irradiations. Time-dose-fractionation relationships developed in pig skin will be tested in pig bladder for both irradiation modalities.

19. BIOCHEMICAL MECHANISMS IN EXPERIMENTAL BLADDER CANCER

Irving, C. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Cancer Research Laboratories, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

The objective of this study was to determine if disulfiram (DSF; tetraethylthiuram disulfide; Antabuse) would influence the induction of bladder cancer in rats given N-butyl-N-(4-hydroxybutyl)-nitrosamine (BHBN). Adult male Wistar rats were divided into four groups as follows: (1) Control diet (Wayne Lab Blox); (2) control diet plus 0.025% BHBN in the drinking water; (3) control diet containing 0.5% DSF; and (4) control diet containing 0.5% DSF plus 0.025% BHBN in the drinking water. The animals were kept on these regimens for 15 weeks and then were transferred to and maintained on control diet. The average total intake of BHBN was 1.21 gm/rat for group 2 and 1.23 gm/rat for group 4. At the time the BHBN was discontinued (15 weeks), the urinary bladders of small numbers of animals in each group were examined and the incidence of bladder cancer was: group 1, 0/3; group 2, 3/9; group 3, 0/3; and group 4, 0/9. At 20-32 weeks (5-17 weeks after the BHBN was discontinued), the cumulative incidence of bladder cancer was: group 1, 0/6; group 2, 48/48 (100%); group 3, 0/6; and group 4, 1/30 (3%). Except for a carcinoma of the renal pelvis in one rat in group 2, no other tumors have been observed in any of these rats. Observation of the remaining rats in groups 1, 3, and 4 (approximately 20/group) continues. It is concluded that DSF has significantly inhibited (p less than 0.001) the induction of bladder cancer by BHBN. The mechanism of action of DSF in this process is under investigation.

20. CULTURE AND CARCINOGENESIS OF HUMAN BLADDER UROTHELIUM

Kaighn, M. E., Kirk, D. L., Shanker, K., Ohnuki, Y., Jones, L. W., Pasadena Foundation for Medical Research, *99 N. El Molino Ave., Pasadena, California*, 91101, United States of America

The basic objective is to develop normal human bladder epithelial cell lines for studies on the mechanism of chemical carcinogenesis. To achieve this goal, culture methods and nutrient media will be designed for this specific cell type. The epithelial nature and normality of isolated cell lines will be established by morphological, ultrastructural, chromosomal and functional properties. Transformation criteria for epithelial cells will be investigated since these differ from those useful for fibroblasts. For system development, direct-acting bladder carcinogens will be employed. The role of promoters, inhibitors and nutritional factors in bladder carcinogenesis will be investigated after the system has been developed and characterized. Although most human cancers are derived from epithelium, most model culture systems are fibroblastic. The system we propose to develop will make it possible to study the action of chemical carcinogens in the appropriate target cell.

21. CYCLIC AMP METABOLISM IN TRANSITIONAL EPITHELIUM

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The morphological time sequence of chemical carcinogenesis in transitional epithelium lining urinary bladder has been characterized in rat models. Due to the microscopically thin nature of the tissue in vivo it has been difficult to conduct physiological, biochemical, and morphological studies that precisely describe and compare the normal mechanisms of growth and differentiation to those of the carcinogenic process. An epithelial growth system which allows the growth, stratification, differentiation, and maintenance of homogeneous, adult Fischer-344 rat transitional epithelium in vitro has been developed. Using this system it is proposed: 1. to further define the requirements and factors governing growth, stratification, differentiation, and maintenance of normal tissue; 2. to determine the biological mechanism of carcinogenesis; and 3. to determine

whether human transitional epithelium will grow and differentiate in the epithelial growth system. The normal tissue studies will include: continued development of a defined media; evaluation of porous growth surfaces; examination of the apparent differentiation-inducing effects of urine; determination of permeability characteristics; and resolution of the role of hormone-stimulated cyclic AMP metabolism in normal tissue. The carcinogenesis studies will include: determination of efficacious carcinogens; definition of morphological staging of in vitro carcinogenesis; assessment of the role of promoters; and analysis of a variety of events important in a two-stage mechanism of carcinogenesis (e.g., dose effects, sequence, reversibility-irreversibility; cell division, etc.). Tumorigenicity of in vitro transformed cell lines will be determined by back-transplantation. The human cell culture studies will utilize remnants of routine bladder punch-biopsies and will be carried out exactly as described for the rat epithelial growth system. These studies are being carried out to lay the foundation for determination of the molecular mechanism of chemical carcinogenesis of transitional epithelium.

BIBLIOGRAPHIC REFERENCES: Minsky, B.D., and F.J. Chlapowski (1978) Morphometric analysis of the translocation of lumenal membrane between cytoplasm and cell surface of transitional epithelial cells during the expansion-contraction cycles of mammalian urinary bladder. J. Cell Biol., 77:685-697. Chlapowski, F.J. (1978) Morphology and cyclic AMP metabolism of normal and spontaneously transformed rabbit transitional epithelium in vitro. Life Sciences, 23:1325-1336.

22. METABOLIC FACTORS INVOLVED IN BLADDER CARCINOGENESIS

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The proposed studies are designed to identify and study metabolic factors involved in carcinogenesis of the urinary bladder in an attempt to meet the goals of the National Bladder Cancer Project. Comparative host metabolism and activation of biologically foreign arylamine derivatives with known or suspected carcinogenic activity will be investigated in susceptible and non-susceptible species by examining the enzyme-mediated molecular level interaction of these carcinogens with critical cellular macromolecules. The in vivo nitrite-dependent diazotization of naturally occurring urinary arylamines with suspected carcinogenic activity will be examined, as well as the carcinogenic activity of the resulting aryldiazonium ions for the rodent urinary bladder, in an attempt to identify agents that may play a causal role in the genesis of human bladder tumors.

23. STUDIES OF MALIGNANT PROGRESSION USING HUMAN CELLS

Smith, H. S., Hackett, A. J., University of California, Berkeley Campus, Lawrence Berkeley Laboratory, Donner Lab., *Berkeley, California,* 94720, United States of America

We propose to determine which parameters known to correlate with transformation in various model systems are applicable to human cancer and at which stage in malignant progression such markers are expressed. To do this, we will develop and characterize syngeneic human epithelial cell lines representing various stages in malignant progression. We will concentrate on carcinomas of the bladder which are frequently found in association with benign lesions. By careful dissection of surgical specimens, we will be able to obtain normal, benign and malignant specimens from the same patient. We will also establish fibroblastic cell lines from the same patients for future studies involving interactions between stromal and epithelial cells. To develop the lines, we will utilize techniques similar to ones that we previously used to establish a series of epithelial cell lines derived from various carcinomatous and nonmalignant human tissue. We will also develop a medium that is more suitable for culturing epithelial cells by determining the optimal nutritional and hormonal requirements for growth of normal, atypical and malignant cells. All of the lines will be characterized for malignant markers defined for various transformation systems including morphology, growth in Methocel and on monolayers, saturation density, invasion of the chorioallantoic membrane, presence of large external transformation sensitive protein (LETSP), ultrastructure by transmission electron microscopy (TEM) and surface morphology using scanning electron microscopy (SEM). To determine which characteristics are retained as cells grow in culture and develop into established lines, we will assay those parameters which can be measured in the primary specimens (TEM, SEM, presence of LETS protein) and all of the parameters as a function of passage.

24. NUTRITIONAL INFLUENCE ON CHEMICAL CARCINOGENESIS

Sidransky, H., Murty, C. N., George Washington University, School of Medicine & Health Sciences, Dept. of Pathology, *2121 Eye St. N.W., Washington, District of Columbia,* 20037, United States of America

The objectives of this proposal are to determine whether a certain dietary component, specifically L-tryptophan, may act as an inhibitor and/or a promoter in chemical carcinogenesis. Chemical carcinogens such as N-2-fluorenylacetamide, ethionine, and 3'-methyl-dimethylaminoazobenzene will be used. The effects of feeding purified diets containing single chemical carcinogens and elevated levels (1%) of L-tryptophan will be determined. Liver and urinary bladder will be evaluated for tumorigenesis and for selected enzyme changes.

25. EFFECT OF DIET ON VESICAL TUMOR AND STONE FORMATION

Gershoff, S. N., McGandy, R. B., Prien, E. L., Ribaya, J. D., Tufts University, Medford Campus, Graduate School, Dept. of Nutrition, *Medford, Massachusetts,* 02155, United States of America

There are two major objectives of this research. One is to study the formation of urinary stones in experimental animals and the metabolic alterations responsible for their production. This will be done using diets of varying vitamin and carbohydrate content with and without added oxalate precursors such as hydroxyproline and glycine.

The other objective is to develop a model for the rapid production of vesical cancer to enhance our ability to study the morphological and metabolic changes associated with the development of this type of cancer. The projected work will study the relationships of diet, carcinogens and initiation of the urinary bladder by foreign bodies on the development of vesical tumors.

BIBLIOGRAPHIC REFERENCES: Ribaya, J.D. and S.N. Gershoff. Interrelationships in rats among vitamin B6, glycine and hydroxyproline. Effects of oxalate, glyoxylate, glycolate and glycine on liver enzymes. J. Nutr. 109:171, 1979. Ribaya, J.D. and S.N. Gershoff. Relationships between hydroxyproline feeding and oxalate excretion in rats fed different levels of vitamin B6. Fed. Proc. 38:452, 1979.

26. ROLE OF SACCHARIN IN BLADDER CANCER

McKenna, T. W., Westat Inc., *11600 Nebel St., Rockville, Maryland,* 20852, United States of America

The objective of this project is to provide information on the possible harmful effects in the area of bladder cancer, resulting from the widespread use of Saccharin.

27. BLADDER CARCINOGENS FROM BRACKEN FERN (RATS)

Pamukcu, A. M., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

28. URINARY BLADDER CARCINOGENESIS BY BRACKEN FERN

Pamukcu, A. M., Bryan, G. T., Ichikawa, M., Erturk, E., Onishi, M., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *450 N. Randall Ave., Madison, Wisconsin,* 53706, United States of America

Bracken fern (BF) is a plant used as a food delicacy and salad green in the United States, Canada, and Japan. The consumption of BF predisposes to an augmented risk for human eosophageal carcinoma. BF is a forage contaminant responsible for a high incidence of naturally occurring bladder cancer in cattle, and intestinal and bladder cancer in sheep. Administration of BF to experimental animals produces a wide variety and high incidence of bladder and intestinal cancer. Carcinogenic

activity of BF can be inhibited by various chemicals. BF carcinogen is excreted in milk of cows fed BF. Such milk produces intestinal and bladder cancer in rats by feeding. Humans ingesting such milk might be unwittingly exposed to a naturally occurring plant carcinogen. BF carcinogen is present in tannin-free extracts of the plant. Such extracts produce a high incidence of cancer in rats by oral administration. Carcinogen present in tannin-free and tumor producing BF extracts will be identified and tested for carcinogenic activity utilizing animal and microbiological systems. Isolation studies of BF carcinogen from milk and urine will be conducted. Bacterial mutagenesis and intestinal and bladder ornithine decarboxylase induction will be used as principal monitors of isolation. Carcinogenesis of bioactive fractions will be studied. The role of L-tryptophan or tannin as promoters of BF carcinogenesis will be investigated.

BIBLIOGRAPHIC REFERENCES: Pamukcu, A.M., Wang, C.Y., Hatcher, J., and Bryan, G.T. Carcinogenicity of tannin and tannin-free extracts of bracken fern (Pteridium aquilinum) in rats. J. Natl. Cancer Inst. (in press), 1980. Pamukcu, A.M. Urinary bladder carcinogenesis by bracken fern. Abstract, National Bladder Cancer Project Workshop, pg. 34-35, 1980.

29. BLADDER TUMORS - INFLUENCE OF DIETARY FACTORS (RATS)

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This is part of a broader project. A summary of this subproject is not available.

3. GENERAL PATHOLOGY AND BIOLOGY

30. THE AGE-ASSOCIATION OF BLADDER CARCINOGENESIS IN MICE - ENZYMOLOGY

Wilson, P., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Enzyme changes in normal and transformed epithelium from young and old mice were studied by electron microscope cyto-chemistry. Alkaline phosphatase was present as an extramembranous cell surface enzyme in basal and intermediate cells but not in full differentiated surface cells. The amount and distribution of the enzyme did not differ between young and old animals. A protein kinase which was cyclic AMP-independent and not inhibited by calcium, was absent from young epithelium but present in old mouse bladder cells and in transformed cell lines derived from them. AMPase and ADPase were lost from the surface of these cells but cyclic AMP-dependent phosphodiesterase and Mg-ATPase were retained. Extramembranous alkaline phosphatase was present in these cells. In transfomed cells derived from a young donor the enzyme was intramemebranous and also associated with mitochondria, endoplasmic reticulum and outer nuclear membranes.

31. EFFECTS OF AGE ON IN VITRO TRANSFORMATION IN THE BLADDER

Franks, L. M., Durbin, H., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

In the earlier papers we have shown that bladder epithelium from old male mice (about 30 months) can be transformed in vitro at a much higher frequency than young epithelium (Summerhayes and Franks, Journal of the National Cancer Institute 1979, 62, 1017) whereas salivary gland epithelium and mesenchyme (Franks and Henzell, European Journal of Cancer 1970, 6, 357) do not show any age-associated differences. We are now repeating these experiments to try to establish when the age effects appear. We are using female mice in some experiments to see whether the bladder tumor incidence is influenced by sex as it is in man. In a further series of experiments we are trying to see whether pure bladder epithelium isolated as described in Report 131 can be transformed alone or on feeder layers. These systems will allow us to analyze the effects of aging on transformation.

32. A STUDY OF THE COLONY-FORMING ABILITY OF HUMAN TUMOR CELLS OBTAINED FROM CLINICAL BIOPSIES

Rupniak, H. T., Hill, B. T., Pritchard, J., Nicholls, J., Laskiewicz, B., Shaw, H. J., Williams, G., Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A cloning assay has recently been described that shows considerable promise as a means of predicting the clinical sensitivity of a patient's tumor by prior screening of that patient's tumor cells against a range of anti-cancer agents in vitro (Salmon et al., New England Journal of Medicine, 1978, 298, 1213).

An ongoing assessment is being made of the feasibility of extending the application of a cloning assay (developed by Courtenay et al., British Journal of Cancer, 1978, 38, 77) to a number of other malignancies. Particular emphasis is being placed on colo-rectal, head and neck, bladder and childhood tumors in collaboration with several hospital units.

By virtue of this ability of tumor cells to clone selectively in soft agar, this procedure also holds promise as a means of establishing human tumor cell lines for in vitro chemosensitivity testing.

33. CLONOGENIC CELLS FROM HUMAN TUMORS

Buick, R. N., Ontario Cancer Inst., Division of Biological Research, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVE: The project objective is to investigate the biological characteristics of in vitro clonogenic cells from human tumors. Those tumors chosen for study are transitional cell carcinoma of the bladder (TCC) and malignant effusions from metastatic carcinoma.

APPROACH: The approach is to analyze factors (in situ-derived and in vitro-derived) which determine clonogenicity, and in addition to assess characteristics such as kinetics, in vitro drug sensitivity and renewal capacity of those cells which are clonogenic.

PROGRESS: Clonogenic assays have been developed for cells derived from human TCC and from carcinoma malignant effusions. The in vitro characteristics of these cells correlate well with the status of the tumor in situ. Evidence has been accumulated to show that host-cell interaction and the choice of semi-solid support are important determinants of clonogenicity.

34. SCHISTOSOMIASIS - BIOLOGY OF SCH. HAEMATOBIUM COMPLEX

Kuntz, R. E., Huang, T., Moore, J. A., Kalter, S. S., Cummins, L. B., Southwest Foundation for Research & Education, *8848 W. Commerce St., Box 28147, San Antonio, Texas*, 78284, United States of America

The main objective of this supplemental proposal is to further explore and describe the biology of Schistosoma haematobium and related mammalian schistosomes in different definitive host-parasite systems. Well established host-schistosome combinations such as golden hamster (Mesocricetus auratus)-S. haematobium and capuchin monkey (Cebus apella)-S. haematobium, will be used as models for continuing investigations on heterologous and homologous immunity. Priority will be given to completion of work on heterologous immunity using Schistosoma rodhaini, a benign rodent schistosome, in hamsters and capuchin monkeys as the immunizing agent and S. haematobium as the challenge. A subproject will consider homologous immunity in capuchins. Moderate (500 cercariae) immunizing infections with S. rodhaini (8-16 weeks) will be followed with S. haematobium challenge infections of greater intensity (2000 cercariae). Data derived from these experiments would be a step toward possible immunotherapy or immunoprophylaxis.

Schistosome characterization and immunity will be judged by a definitive host-parasite picture consisting of: (1) parasite returns and distribution, (2) distribution and intensity of tissue egg deposits, (3) condition of parasites in different host organs, (4) intrauterine egg counts, and (5) pathology. S. haematobium infection in the capuchin monkey subjected to a homologous immune situation will allow evaluation of this aspect of pathobiology, possibly related to bladder carcinogenesis. The status of schistosomiasis in primates will be determined in part by excreta egg passage patterns, urine cytology to detect urothelial alterations, and X-ray.

BIBLIOGRAPHIC REFERENCES: Species specificity of the intermediate hypersensitivity to schistosomal proteolytic enzyme. A. W. Senft, J. K. Weltman, L. G. Egyud, M. B. Goldgraber and R. E. Kuntz. Parasite Immunology 1:1-11, 1979. Distribution of eggs/lesions in nonhuman primates infected with S. haematobium. R. E. Kuntz, J. A. Moore and T. C. Huang. J. Medical primatology 8:167-178, 1979.

35. CELL SURFACE CHANGES IN TRANSITIONAL CELL TUMORS

Limas, C., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pathology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The proposed studies explore the possibility of a relationship between changes in the cell surface properties of transitional cell carcinomas (TCC) of the urinary bladder and the clinical course of the disease. Detectability of ABH and T antigens, agglutinability by lectins, and sialic acid content of the tumors will be correlated with biological behavior (in particular, frequency of recurrences, invasiveness, and metastases) in an attempt to assess the prognostic significance of such parameters. The mechanism by which cell surface changes are brought about will be studied by following the activities of enzymes involved in the synthesis of ABH substances (glycosyltransferases) and their degradation (glycosidases). Tumor and serum sialyltransferase activities and sialic acid levels will be tested to investigate possible correlations with the course of the disease. It is hoped that these studies will provide important information about the biological behavior of TCC and may provide a means of assessing the prognostic outlook of patients with such tumors.

36. GEOGRAPHICAL DIFFERENCES IN TRYPTOPHAN METABOLISM OF PATIENTS WITH BLADDER CANCER

Brown, R. R., Wolf, H., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *450 N. Randall Ave., Madison, Wisconsin*, 53706, United States of America

The aim is to study the incidence of abnormal tryptophan metabolism in bladder cancer patients in urban Copenhagen in comparison with patients from rural Wisconsin.

37. PERMANENT CELLULAR ALTERATION OF BLADDER EPITHELIUM

Cunha, G. R., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Anatomy, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

38. PROLIFERATIVE METAPLASTIC AND IN SITU NEOPLASTIC LESIONS OF THE BLADDER

Mostofi, F. K., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia*, 20306, United States of America

The work on precancerous and in situ carcinomas of the bladder is continuing. The ABO agglutination test has been applied to 30 in situ carcinomas of the bladder, and we are working on the others and correlating the findings with progression of the disease.

Follow-up on cases of nephrogenic adenoma and glandular cystitis continues.

39. LOCAL REGULATION OF INVASIVENESS IN BLADDER TUMORS

Pauli, B. U., Kuettner, K. E., Rush University, School of Medicine, Dept. of Pathology, *1725 W. Harrison St., Chicago, Illinois*, 60612, United States of America

Malignant tumor cells are invasive by degrading such host barriers as basal lamina and connective tissues. Since collagen constitutes the primary component of these barriers, invasiveness must involve the degradation of collagen. We propose that this is achieved by the elaboration of specific collagenolytic activity from the invading cells. Nevertheless, certain connective tissues such as hyaline cartilage resist invasion. This selective resistance to invasion is obviously determined by tissue specific anti-invasive principles which may express themselves as a physical barrier to invasion or a system translated into the specific inhibition of the penetration by tumor cells. Indeed, cartilage contains a low molecular weight protease inhibitor (5) which is able to inhibit collagenolytic activity and which after extraction makes the cartilage penetrable to tumor cells. Similar protease inhibitors have since been found in other connective tissues including bovine urinary bladder.

In this proposal, we shall study the concept of collagenolytic activity as a proximal event in the acquisition of an invasive potential by tumor cells and define interrelationships between tumor protease (collagenase) activity, host protease (collagenase) inhibitor(s), and tumor growth characteristics in cell lines derived from chemical carcinogen (FANFT)-induced transitional cell carcinomas arising in the urinary bladder of the Fischer rat. The FANFT-model is particularly well suited for the goals of this proposal, since FANFT tumors pass through a well defined and reasonably long preinvasive stage of development before becoming invasive; thus, allowing the study of cells derived from preinvasive and invasive bladder tumors.

40. BLADDER CANCER - MENISCUS GRADIENT AND MATRIX CULTURE

Leighton, J., Abaza, N. A., Tchao, R., Johnson, W. D., Butt, M. R., Murphy, J. J., McCormick, J. F., Schroyens, W., Nicosia, R., Medical College of Pennsylvania, School of Medicine, Dept. of Pathology, *3300 Henry Ave., Philadelphia, Pennsylvania*, 19129, United States of America

Our technique, histophysiologic gradient culture, is a simple in vitro procedure in which epithelial cells alone or in combination with stroma proliferate as a tissue of many cell layers on a diaphragm of collagen, where both attachment and complete nutrient exchange including oxygen take place at the same surface.

We will extend our earlier studies on human bladder cancer, normal rat bladder, and rat bladder cancer. As one part of this research we will study certain specific supracellular phenomena that are components of destructive invasion by cancer.

BIBLIOGRAPHIC REFERENCES: Leighton, J., Tchao, R., Stein, R., and Abaza, N. Histophysiologic Gradient Culture of Stratified Epithelium, a chapter in Cultured Human Tissues and Cells in Biomedical Research, Vol. IIB, in the series Methods and Perspectives in Cell Biology, D. Prescott, ed., Academic Press, NYC 1980, in press. Leighton, J. and Butz, D.E. Plastic Apparatus for Standardized Histophysiologic Gradient Culture (abstract). In Vitro, 16: in press, 1980.

41. DEVELOPMENT OF A CYTOMETRIC DATA BANK

Sadier, E., Guman, N., Hospital Interzonal Mariano Castex, Servicio de Patologia, *Balcarce 900, 1650 San Martin, Buenos Aires, Argentina*

OBJECTIVE: To register cytometric data (nuclear and cytoplasmic diameters and size and percentage of micro- and macronucleoli) and cytomorphological data on histologic sections and cytologic specimens from approximately 600 malignant and benign tumors, hyperplasias, normal controls, etc.

This will provide data for an Automated Cellular Diagnostic System, and, during its development, will allow study of detailed classification of malignant tumors, relationship between tumors and preneoplastic atypias, oncogenic processes, etc.

METHOD: An ocular micrometer and immersion oil objective (1875 x) will be used in determining measurements and cytologic characteristics. The data will be processed electronically to obtain the arithmetic mean, standard deviation, and standard error and variance; they will be verified with the Student Test and Analysis of Variance. The results will be recorded on perforated cards.

PROGRESS: Data are complete on 1) colon adenomas, 2) endometrial hyperplasias, 3) cervical dysplasias and carcinomas in situ, 4) transitional cell carcinomas, papillomas and hyperplasias of the bladder, 5) basal hyperplasias and bronchial metaplasias, 6) non-Hodgkin's lymphomas, 7) nevi and melanomas, 8) canalicular breast carcinomas, 9) endometrial adenocarcinomas, 10) prostatic adenocarcinomas, 11) gestational endometrial hyperplasias, 12) colon adenocarcinomas, 13) gallbladder adenocarcinomas, 14) gastric adenocarcinomas, 15) atypias in chronic gastritis, 16) hepatomas, 17) skin basal cell epitheliomas, and 18) invasive squamous cell carcinomas of uterine cervix.

42. NBCCGA - CENTRAL CYTOLOGY AND PATHOLOGY LABORATORY

Friedell, G. H., St. Vincent Hospital, *25 Winthrop St., Worcester, Massachusetts*, 01604, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

This application covers the proposed activities of the Central Pathology Laboratory.

43. PROFESSIONAL EDUCATION IN CYTOLOGY

Barker, E. A., University of Washington, School of Medicine, Dept. of Pathology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

OBJECTIVE: Provide a three-year agreement to develop and conduct an educational training program to advance the use and value of cytology in bladder, lung, colorectal, and cervical cancer. The Contractor is required to develop and conduct this training program; in addition, to participate in the Steering Committee Meetings, provide semi-annual written reports of progress and problems, provide written preliminary final report to be submitted for review by the Project Officer, and submit revised final report based on Project Officer's review of preliminary report.

B. RENAL AND UROLOGICAL SYSTEM

1. INDUCTION BY CHEMICALS

44. HORMONE INDUCED AND DEPENDENT TUMORS

Villee, C. A., Lin, Y. C., Brennessel, R. A., Harvard University, Boston Campus, School of Medicine, Dept. of Biological Chemistry, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The objectives of the proposed research are to exploit the new model system of the renal adenocarcinoma transplanted under the kidney capsule of the estrogen implanted hamster to determine (1) the mechanism of estrogenic tumorigenesis in the kidney, bladder and pituitary, (2) the nature of hormone dependency of the tumor cells, and (3) the changes involved as the tumor is transformed from the hormone-dependent state to the autonomous state. We plan to investigate how estrogenic induction and maintenance of tumors differ from the mechanism by which estrogen stimulates its target organs such as the uterus. A further objective is to understand the mechanism by which progesterone and antiestrogens, clomiphene and nafoxidine, protect the kidney against tumorigenesis. The pituitary of the estrogen implanted hamster undergoes hyperplasia, increases its content of progesterone receptors some seven-fold and finally becomes tumorous. We plan to determine what relationship, if any, exists between the hypertrophy of the pituitary and the neoplastic transformation of the kidney in the estrogen implanted hamster. Using hypophysectomized hamsters bearing DES implants and having renal tumors transplanted under the kidney capsule, we will investigate the possible role of the pituitary and its hormones in inducing and maintaining the renal adenocarcinoma. Does the pituitary secrete some factor required in the carcinogenic process or one that plays a permissive role in tumorigenesis? Experiments paralleling the ones in vivo will be carried out using cell cultures of renal and pituitary tumors and studying the effects of prolactin, ergocornine, gonadotropins and anti-FSH and anti-LH on their growth and regression. We plan to develop an autonomous kidney tumor by serial passages of the estrogen dependent tumor tranplanted under the kidney capsule. We plan to investigate the role of estrogen receptors and progesterone receptors in tumorigenesis and in protecting tissues against tumorigenesis using not only the kidney but also the pituitary and bladder of the hamster. These studies should provide improved understanding of the mechanism by which steroids support or inhibit growth of hormone dependent tumors such as tumors of the breast, endometrium and prostate in the human.

BIBLIOGRAPHIC REFERENCES: Lin, Y.C., Talley, D.J., and Villee, C.A.: Increased Progesterone Receptor Concentrations in Bladder Lesions of Estrogen-Treated Syrian Hamsters, Cancer Research 39; 2614-2617, 1979. Villee, C.A. and Loring, J.M.: Hormonal Control of Testicular Enzymes (Abstract, Endocrine Society, Anaheim, Calif., 1979), in press.

45. ESTROGEN CARCINOGENICITY AND HORMONE DEPENDENT TUMORS

Li, J. J., Li, S. A., Klicka, J. K., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The overall objective of the proposed research is to continue to use the hamster estrogen induced and dependent renal carcinoma as a model to study estrogen carcinogenicity, tumor hormone dependency, and transition of estrogen tumor dependency to autonomy. The significance of steroid receptors in human renal carcinomas will also be assessed. Our aim is to focus our research effort on the 4 areas where information is much needed. First, to elucidate the mechanism of estrogen carcinogenicity and the effect of other steroids and antihormonal agents on this process in the hamster kidney. Our goal is to determine if estrogen carcinogenesis can be affected by known carcinogenic inhibitors; the effect of estrogens on P-448, 450, BP-hydroxylase, epoxide hydrase, glutathione-S-transferase, and peroxidase activities in the hamster kidney and liver; the ability of estrogen intermediates to induce renal tumors in the hamster; to identify metabolites of estrogens derived from hamster kidney and liver microsomal and cell suspension incubations following separation on HPLC and to assess the ability of these metabolites to bind covalently to purified DNA and chromatin; and to seek markers of estrogen action in the untransformed kidney. Second, our demonstration that all major classes of steroid receptors reside in the hamster kidney tumor provides a unique system to study the hormonal interrelationships involved in tumor response to endocrine therapy within a single tissue. Tumor cell suspension and tumor slice preparations will be used to study the effect of various steroids and antihormones, used singly or in combination, on RNA and protein synthesis. Studies will be undertaken to identify the chromosomal site (acceptor site) for each steroid receptor complex using partially purified tumor receptors. Third, autonomous tumor variants will be used to determine the nature of the dissociation between progesterone receptor regulation and autonomous tumor growth. Fourth, both cytosol and nuclear steroid receptors in the human renal tumor and effects of steroids on RNA synthesis in human tumor slices will be studied.

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46. ROLE OF HORMONES IN RENAL CELL CANCER IN THE HAMSTER AND HUMAN

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The overall objective of the research is to continue to use the hamster estrogen induced and dependent renal carcinoma as a model to study estrogen carcinogenicity, tumor hormone dependency and transition of estrogen tumor dependency to autonomy. The significance of steroid receptors in human renal carcinomas is being assessed. We are focusing our research effort on these 4 areas where information is much needed: 1) To elucidate the mechanism of estrogen carcinogenicity and the effect of other steroids and antihormonal agents on this process in the hamster kidney. Our goal is to determine if estrogen

carcinogenesis can be affected by known carcinogenic inhibitors; the effect of estrogens on P-448, 450, BP-hydroxylase, epoxide hydrase, glutathione-S-transferase, and peroxidase activities in hamster kidney and liver; the ability of estrogen intermediates to induce renal tumors in the hamster; to identify metabolites of estrogens derived from hamster kidney and liver microsomal and cell suspension incubations following separation on HPLC and to assess the ability of these metabolites to bind covalently to purified DNA and chromatin; to seek markers of estrogen action in the untransformed kidney. 2) We have demonstrated that all major classes of steroid receptors reside in the hamster kidney tumor; this provides a unique system to study the hormonal interrelationships involved in tumor response to endocrine therapy within a single tissue. Tumor cell suspension and tumor slice preparations are being used to study the effect of various steroids and antihormones, used singly or in combination, on RNA and protein synthesis. Studies are under way to identify the chromosomal site (acceptor site) for each steroid receptor complex using partially purified tumor receptors. 3) Autonomous tumor varients are being used to determine the nature of the dissociation between progesterone receptor regulation and autonomous growth. 4) Both cytosol and nuclear steroid receptors in the human renal tumor and effects of steroids on RNA synthesis in human tumor slices will be studied.

47. MECHANISM OF ESTROGEN-INDUCED RENAL CARCINOGENESIS

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In this research project we will study the chemical mechanism of estrogen induction of renal clear cell carcinomas in Syrian hamster. It has been shown that among the steroid hormones tested, estrogens alone are capable of inducing these kidney tubule tumors, and that the induction is tissue specific in that only kidney tumors develop and not tumors in other tissues. Natural and synthetic estrogens are equally potent in tumor induction. Our purpose is to establish the molecular basis for the tumor induction by; (1) studying the metabolism of diethylstilbestrol in hamster, identifying and characterizing these metabolites, (2) determining whether allylic alcohol metabolites or semiquinone-quinone metabolites are the active adduct forming compounds with the bases of DNA, (3) determining whether the inactive (congugated) metabolites are delivered to kidney, followed by subsequent activation by deconjugation, (4) determining the nucleoside specificity of adduct formation (i.e., guanosine, adenosine, thymidine, or cytidine) (5) establishing if adduct formation by any diethylstilbestrol metabolite correlates with carcinogenicity, and (6) establishing the chemical structures of adducts by separation with high pressure liquid chromatography, followed by mass spectrometry procedures and NMR analysis. Finally, attempts will be made to block diethylstilbestrol carcinogenesis with reducing substances which may react with the active metabolites blocking their carcinogenic activity.

The overall goal of this project is to establish that diethylstilbestrol can function as a DNA altering material similar to other chemical carcinogens, and to begin to explore the chemical nature and frequency of specific DNA base adducts.

48. ENDOCRINE FACTORS IN TUMOR PROMOTION

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The effects of hormones on the induction of ornithine decarboxylase (ODC), S-adenoxylmethionine decarboxylase (SAMDC), and polyamine levels in vivo are being studied. Previous studies have shown that ODC induction may be a marker for tumor promoters. Hormones often increase the biological activitives of complete carcinogens. ODC is used to study the degree of biochemical similarity between hormones and promoters. The present studies indicate that estradiol induces renal ODC and SAMDC in both the rat and hamster. The induction of renal ODC in the rat by estrogens is proportional to their binding in vitro to cytoplasmic estradiol binding sites. ODC levels in the ovary and uterus of female rats are inversely correlated with each other. Estrogens as potential promoters will be tested in two-stage initiation-promotion carcinogenesis studies.

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49. MULTI-STAGE RENAL CARCINOGENESIS IN RATS

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The proposed research is designed to determine the multistage progression and nature of renal carcinogenesis. Additional objectives are: Delineation of the relationship betweeen presumptive premalignant and malignant, N-(4'-fluoro-4-biphenyl)acetamide (FBPA)-induced renal cortical lesions and evaluation of the biological nature and behavior of presumptive premalignant renal cortical lesions by histochemistry, light microscopy and x-ray microanalysis. In phase I, male Fisher 344 rats will be fed a diet containing FBPA (0.04% w/w) for different lengths of time from 8 to 65 weeks. Group A will receive continuous feeding of FBPA as a positive control. Group B will be fed a control diet. Group C will be fed the FBPA diet for varying times then placed on the control diet to assess the reversibility of induced lesions. Group D will be fed FBPA for 8 or 16 weeks then be fed a potential promoter, NTA or injected with TCDD to assess promotion of early lesions. Presumptive premalignant and malignant lesions throughout these studies will be characterized by histochemistry, light microscopy and x-ray microprobe techniques. In phase II rats will be injected with 1 dose of FBPA followed by chronic treatment with TCDD or NTA in experiments designed to assess the multi-stage nature of FBPA-initiated renal carcinogenesis. Gross and microscopic lesions in animals from all protocols will be quantified by accepted techniques and statistical analysis will be performed between appropriate groups.

50. METHOTREXATE-INDUCED NEPHROTOXICITY AND DRUG DEVELOPMENT

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Our studies of the mechanism and localization of the renal tubular methotrexate (MTX) transport in Rhesus and Cynomolgus monkeys and rats have been continued. Stop-flow experiments in the monkey have clearly demonstrated that MTX undergoes tubular secretion by a mechanism which is localized mainly in the proximal tubule. The ratio of U/PMTX to U/Pinulin was above one throughout the nephron; thus no tubular reabsorption was suggested. Simultaneous injection of folic acid or folinic acid had no effect on the excretory pattern of MTX. However, simultaneous administration of PAH blocked the tubular secretion of MTX and lowered the U/PMTX to U/Pinulin ratio throughout the nephron; a peak U/PPAH ratio of 14 was observed in samples corresponding to the proximal tubule. Histological studies of MTX-exposed kidneys showed profound vacuolation of the proximal tubular cells but few vacuoles in the distal tubular cells as compared with the normal kidney. The uptake of MTX by monkey renal cortical slices in the presence of different substrates was studied. It was found that folic acid and folinic acid had no effect on MTX uptake, confirming our in vivo data. However, PAH and aspirin depressed MTX uptake by at least 50% and 2,4-DNA inhibited uptake by 78%. In the presence of amphotericin B or vincristine, the cortical uptake of MTX was augumented. The mechanism of this augmentation is under further investigation.

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51. TRANSPLACENTAL EFFECTS OF NITROSO COMPOUNDS

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We are analyzing the chronic transplacental carcinogenic effects of nitroso compounds in inbred strains of mice and rabbits. These effects depend greatly upon the hereditarily determined differences in susceptibility or resistance of pregnant mothers and embryos, and the stage of fetal (organ) development. Examples are the transplacental induction of primay renal tumors in rabbits, the transplacental effects of diethylnitrosamine in mice as related to strain of mice (genotype) and day(s) of administration during pregnancy, etc. We are also interested in the effects of chemical and viral (type C genomes) interaction in the fetuses.

52. QUANTITATIVE ALKYLATION OF NUCLEIC ACIDS BY CARCINOGENS

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The hypothesis that N-nitroso compounds are carcinogenic because they are converted to direct alkylating agents by only target tissues is attractive, but most studies designed to test the hypothesis have investigated formation of alkylated bases only after a single administration of a near lethal dose of carcinogen which may be pharmacokinetically unrelated to environmental exposures. Proposed studies will continue to examine quantitatively the chemical nature and extent of alkylation of DNA in liver, kidney, lung, pancreas, and colon by five carcinogens which are converted to alkylating agents at widely different rates by these tissues. Sensitivities of these tissues to carcinogenic activities of 1,2-dimethylhydrazine, diethylnitrosamine, N-nitrosopyrrolidine, N-nitrosomorpholine, and methylnitrosourea are established and are being used as comparators with site of alkylation. Adult rats and hamsters will be given single doses of diethylnitrosamine ranging from 1/16 to 1 LD50 and ethylation of DNA will be quantitated over the following 216 hrs. A similar study will be conducted with methylnitrosourea in guinea pigs. Also, ethylation of DNA during chronic administration of low levels of diethylnitrosamine to rats will be measured in target and non-target tissue. Isolation, silylation, and gas chromatography-mass spectrometry analysis of newly detected DNA adducts in N-nitrosopyrrolidine- and N-nitrosomorpholine-treated rats will be pursued.

53. PERSISTENCE OF ALKYLATED DNA IN CARCINOGENESIS

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The aim of the research is to discover the underlying reactions responsible for the carcinogenicity of nitroso compounds and to ascertain whether there are protective mechanisms by which the cell can minimize the damage produced by these agents. The hypothesis that carcinogenesis is due to the formation and persistence in DNA of the promutagenic base, 06-methylguanine, is being studied. The reactions responsible for the formation of, and subsequent loss of this product are being studied in a number of different tissues known to differ in their susceptibility to the carcinogenic insult produced by the nitrosamines. At present, all of the data collected is consistent with the hypothesis and it appears that the relative resistance of the liver to carcinogenesis is due to the high efficiency with which this abnormal purine can be removed from liver DNA.

The studies are being carried out using dimethylnitrosamine which produces liver and kidney tumor in rats, N-methyl-N-nitrosourea which produces tumors in the neurons system and in other organs and 1,2-dimethylhydrazine which gives rise to tumors in the colon.

The enzyme responsible for the removal of 06-methylguanine from rat liver has been partially purified and the properties of this enzyme are currently under investigation using DNA isolated from dimethylnitrosamine-treated rats as a substrate.

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54. EXPERIMENTAL PATHOLOGY OF RENAL CARCINOGENESIS

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The objective of the proposed research is to identify the sequential stages of tissue and cellular events which occur during the induction of renal neoplasia by nitroso compounds and to develop further cell culture models which will provide information that will correlate directly with the in vivo process. Emphasis will be placed on the identification of target cells and their responses to carcinogens, and on the identification of precursor lesions and their progression, utilizing techniques of isotopic labeling and electron microscopy. Cell cultures derived from carcinogen-treated animals will provide simpler experimental systems facilitating the analysis of target cells in terms of their ultrastructural, proliferative, biochemical and functional characteristics and of the stages in the transformation process. Additionally, it is proposed to seek and test for modifying factors effective in the tumor systems and to investigate their mode of action in the pre-determined stages of renal tumor induction. The broad objectives of the project are to further the understanding of the basic biology of human renal neoplasia and of the process of chemical carcinogenesis in general, and to identify strategies which may reverse or inhibit the cancer process.

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55. NICKEL CARCINOGENESIS

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The long term objective of this research program is to elucidate the mechanisms of carcinogenesis by nickel compounds. The specific aims of this proposal are: (a) to investigate the inhibitory effect of manganese upon the carcinogenicity of nickel subsulfide (alpha-Ni3S2); (b) to identify the metabolic basis for the pronounced differences which have been found between the carcinogenicities of alpha-Ni3S2 and nickel sulfide (NiS); and (c) to characterize and standardize an experimental system for induction of renal carcinomas in rats by intrarenal injection of alpha-Ni3S2. The methods include: (a) carcinogenesis testing following administration of alpha-Ni3S2, NiS, Mn and other compounds to Fischer rats by intramuscular and/or intrarenal injection; (b) histological and electron microscopic investigations of pathological lesions that are associated with induction of renal carcinomas by alpha-Ni3S2; and (c) compartmental analysis of 63Ni and 35S kinetics in order to identify differences in the metabolism of radiolabelled alpha-Ni3S2 and NiS in rats. This study is providing fundamental knowledge of metal carcinogenesis and is also furnishing information which has practical applications to assessing human hazards of carcinogenesis from nickel compounds, with particular relevance to energy research, industrial toxicology and environmental pollution.

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56. EXPERIMENTAL TOBACCO CARCINOGENESIS

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OBJECTIVE: The determination of toxic, mutagenic, carcinogenic and cocarcinogenic constituents of tobacco smoke through chemical analytical methods and bioassays is established as a basis for attempts to reduce the levels of such compounds in tobacco smoke. Special emphasis is placed on the study of mechanisms of action of tobacco-specific cocarcinogens in the weakly acidic and neutral subfractions of the smoke particulates and the biological effect of flavor additives in the smoke of low 'tar', low nicotine, low carbon monoxide cigarettes.

APPROACHES: Screening for biological activities includes testing of isolated and model compounds in mutagenicity tests on bacterial tester strains TA 98 and TA 100, as well as rate of metabolic activation of BaP-3H in mouse epidermis.

CURRENT PLANS AND/OR PROGRESS: A systematic identification of aromatic nitro compounds in cigarette smoke is planned with subsequent determination of mutagenic and other biologic activities.

The carcinogenicity and the presence in blood and urine of nitrosated nicotine metabolites will be explored in order to delineate the correlation between tobacco smoking and cancers of the urinary tract in an experimental setting. Model studies with 14C-labelled nicotine metabolites will be designed to explore the possibility of in vivo nitrosation.

57. STUDIES OF CARCINOGENESIS IN HUMAN TISSUES

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OBJECTIVES: Obtain viable normal tissue, with intact urothelium supported by mesenchyme, from human bladders, normally by transurethral biopsy of patients being examined for suspected urinary tract disease, but occasionally from cystectomy specimens freshly removed in the course of treatment. Establish long-term in vitro organ cultures of such normal human bladder explants, and establish cell cultures in parallel, if possible. Determine the parameters for normal growth of human urothelium in vitro in organ culture by comparison with parameters already established for rat bladder explants in vitro, and rat and human bladder in vivo. Apply methods of experimental carcinogenesis, already developed in vivo and in vitro for the rat, to the induction of carcinogenesis in human bladder explants cultured in vitro and to study the changes in the parameters as established above.

58. MECHANISMS AND MANIFESTATIONS OF CARCINOMATOUS CHANGE IN HUMAN AND EXPERIMENTAL CANCER

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The research reported covers a multidisciplinary program for the early diagnosis of human cancer and for studying metastatic properties of cellular attachment. The attachment of epithelial cells and of fibroblasts to surfaces was studied by a newly modified reflexion contrast microscope. The malignant potential of cervical condylomata accuminata was assessed in a patient population of 190,000 well women. A third study concerns the identification of primary human breast cancers with their metastases using quantitative measurements of individual cellular DNA distribution. A fourth study has been involved in establishing new morphometric and cytochemical markers for highly differentiated urothelial cancers. The potential of fine needle aspiration biopsy for obtaining new parameters for estimating prognosis and further diagnosis of primary and secondary human cancers was explored. A continuing study of carcinogen metabolism included effects of anti-oxidants on metabolism of polycyclic aromatic hydrocarbons. A study of the kinetics of cellular growth in cervical epithelium was conducted to determine the viability of cervical epithelium after exposure to carcinogens.

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59. THE INFLUENCE OF IMMUNE STATUS ON CARCINOGENESIS BY NITROSO CARCINOGENS

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OBJECTIVE: Firstly, to determine whether the production and development of some chemically induced tumors are correlated with variations in immunological status. Secondly, to attempt to relate early and late stages in tumorigenesis to the development of cell-mediated and humoral immune responses.

APPROACH: For the first objective, methods for producing long-term immunosuppression in rats will be investigated. Conventionally housed, inbred thymectomized rats will be given various schedules of lethal X-or gamma-irradiation with immediate reconstitution with bone marrow. A second group of rats will be given daily antilymphocyte globulin (ALG) combined with large doses of cytosine arabinoside (Ara-c). Treatment lasts for 3 weeks. Immune status will be tested by allogeneic skin grafting, lymphocyte transformation, spleen plaque cell formation, hemagglutination, and rosette formation. LD50 tests for dimethylnitrosamine (DMN) will be carried out in rats of the second group. For the second objective, the immunlogical response of rats with different tumor loads of a DMN-induced kidney tumor and of a spontaneously appearing transplantable kidney tumor (Eker renal adenoma rat) will be tested by lymphocyte transformation, plaque cell formation, hemagglutination, rosette formation, migration inhibition and lymphocytotoxicity against dispersed tumor cells carried out in diffusion chambers.

PROGRESS: Rats were effectively immunosuppressed by irradiation but life-survival could not be extended in most cases beyond about 4 weeks. ALG plus Ara-c treatment has produced immunosuppressed rats, most of which have carried viable skin grafts for a variable period between 3 to 14 months. These rats were bred in this Institute. However, all rats of a second strain bought commercially died of chronic respiratory infection soon after immunosuppressive treatment had ceased, in spite of continuous administration of oxytetracycline in the drinking water. The well-established dichotomy in the LD50 for DMN between normal rats fed a protein-free diet or a normal diet was not observed in rats immunosuppressed with ALG and Ara-c.

Rats with inherited kidney tumors did not show a clear correlation between an increasing tumor load and an expected decreased immune response. Some rats with enormous tumors still produced a good T-cell and B-cell response. (Text Abridged.)

2. ROLE OF VIRUSES

60. MONITORING OF HERPES SIMPLEX VIRUS TUMOR-ASSOCIATED ANTIGENS IN HUMAN MALIGANT NEOPLASIAS

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The detection of HSV nonvirion antigens in selected tumors as expression of a repressed viral genome proves a continuing release of virus specific messages and supports an important role of the virus in the development of the tumor.

The purification of nonvirion antigen induced by HSV facilitates the detection of antibody for HSV nonvirion antigens in patients with certain cancers without absorption of their sera with HSV virion antigens. Furthermore, the preparation of specific antibody for these special antigens (nonvirion) is now relatively at hand in many laboratories for the investigation of the immune response of cancer and control populations.

PURPOSES AND AIMS: 1. To obtain purified preparations of HSV tumor-associated ('nonvirion') antigens (TAA) for use in radioimmunoassay and ELISA with cancer and control sera. 2. To monitor the presence of specific TAA antibodies in patients with different tumors of the oral and urogenital tract. 3. To correlate the clinical stage of the neoplastic disease with the presence of antibody to HSV-TAA. 4. To determine the difference in the amounts of HSV-TAA antibody between pre-operative patients and those clinically cured.

61. MH2 AND MC29 VIRUSES - CARCINOMA ONCOVIRUSES

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Two avian retroviruses, namely MH2 and MC29, are capable of causing liver carcinoma and kidney nephroblastoma in chickens a few days after infection. The avian model provides an excellent model for use in studying pathological events of carcinoma since this is the first time that C particles are being found to cause such an important disease. Our study was first focused on the response of the chicken to the two viral strains followed by an analysis of the similarities and differences between the two viruses. At present, we are attempting to determine which target cell is responsible for the oncogenic response and at what stage of differentiation the transforming process may initiate.

62. NEOPLASTIC TRANSFORMATION INDUCED BY AMV

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This laboratory has been engaged for several years in trying to solve the mechanism of leukemic infection by some RNA tumor viruses in the chicken. This experimental model may hopefully serve as a guideline to the yet unsolved problem of human leukemia. Although avian myeloblastosis virus (AMV) has been used as our major tool for these studies, we have recently started to investigate the effect of other avian tumor viruses which are capable of inducing additional oncogenic disorders, such as liver and kidney carcinoma, besides acute leukemia. These complex tumor manifestations do reflect a general assumption that these viruses are capable of interfering with the normal pathway of cell differentiation and that specific target cells may be present in hemopoietic tissues for each leukemia virus. To identify these cells and their role in the leukemic processes is the goal of this laboratory.

63. RELATION OF INFECTION WITH HEPATITIS B AGENT TO NEOPLASIA IN PATIENTS WHO HAVE RECEIVED KIDNEY TRANSPLANTS

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Patients who received renal transplants have a high incidence of malignant tumours, particularly reticulum cell sarcoma. A prospective study is being undertaken to determine whether the pretransplant presence of HBsAg or anti-HBs has any effect on the subsequent development of tumors.

64. VIRUSES IN GENITOURINARY MALIGNANCY

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The purpose of efforts this last year has been to expand our studies with the in vitro chemotherapy testing and to determine whether or not in vitro and in vivo data correlate. Two long-term studies have been conducted. Two renal adenocarcinomas obtained at surgery were implanted in athymic (nude) mice where they produced two distinct mice, 10478 and 14877, which could be maintained by serial passage. Tumors were harvested, dispersed with 1% collagenase and seated in microtiter wells at a concentration of 25,000 cells/well. To each well was then added growth media, radio label precursor substances and selected chemotherapeutic agents. After seven days, the cells were harvested and the amount of radiolabel incorporated was assayed to determine the potential of each agent to produce cell kill. The agents most effective in vitro against tumor cells 10478 were Cis-platinum, adriamycin and Vinblastine, in order of decreasing effectiveness, and against tumor cells 14877 were Adriamycin, Cis-platinum, Vinblastine, in order of decreasing effectiveness. Tumors 10428 and 14877 were implanted in a series of athymic mice and, after four weeks of growth, when the tumor measured between six and 10mm, treatment with the above agents was begun. The agents capable of reducing tumor 10478 were, in order of decreasing effectiveness, Cis-platinum, Adriamycin and Vinblastine. The agents producing cell kill in tumor 14877 were, in order of decreasing effectiveness, Adriamycin, Cis-platinum and Vinblastine. Eleven additional renal adenocarcinomas have been removed in surgery and the chemotherapy sensitivity profiles for each determined in vitro as noted above. Each tumor possesses a distinct sensitivity profile. The data would indicate that the in vitro assay data demonstrate a difference in chemotherapeutic sensitivity spectrums between human renal adenocarcinomas and that this test also predicts which agents are most effective and which agents are least effective in the tumor bearing host.

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65. PROBLEMS OF DISEASES CAUSED BY HERPESVIRUSES, ESPECIALLY PROBLEMS UNDERLYING LATENCY AND ONCOGENESIS

Rapp, F., Geder, L., Isom, H., Tenser, R., Tevethia, S. S., Marquez, E. D., Tevethia, M. J., Howett, M. K., Hyman, R., Taylor, J. M., Pennsylvania State University, Milton S. Hershey Medical Center, School of Medicine, Dept. of Microbiology, *500 University Dr., Hershey, Pennsylvania*, 17033, United States of America

We have assembled a group of investigators from different disciplines to focus on the problems of disease caused by herpesviruses, especially problems underlying latency and oncogenesis. Several herpesviruses of animals and man have been chosen to study differing aspects of the ability of these viruses to cause latent infection and to transform cells to malignancy. We hope to determine under what conditions latency and reactivation of these viruses occur, the molecular events required to initiate and maintain the transformed state of mammalian cells, the events that influence the ability of the transformed cells to metastasize, and the role of these viruses in neoplastic disease of the human urogenital tract. Studies concerning the transformation of human and other cells by herpesviruses will be conducted by Dr. Fred Rapp. Attempts to delineate the gene and gene products that are responsible for initiation and maintenance of the transformed state will be conducted by Dr. Mary K. Howett. Dr. S. S. Tevethia will examine the involvement of herpes simplex virus (HSV) glycoproteins in cell-mediated immune cytolysis. Dr. Marquez's efforts will be to characterize these HSV glycoproteins in immune complexes. Drs. Geder and Hyman will study infectious bovine rhinotracheitis virus to determine whether the genes responsible for transformation by this virus share sequences with human cytomegalovirus (CMV) and whether there are common genes required for transformation. Dr. Mary Judith Tevethia will attempt to genetically characterize the CMV genome, including gene(s) required for in vitro transformation of mammalian cells. Cloning of HSV and CMV DNA fragments is being supported by Dr. John Taylor. The guinea pig and its cells are being used as a model system by Dr. Harriet Isom, who plans to study transformation using guinea pig CMV, and Dr. Richard Tenser, who will study latency. A direct attack on the problem of etiology of human neoplastic diseases by herpesviruses will be carried out by Dr. Hyman to determine whether herpesvirus nucleic acids are present in human cancer tissues.

66. SEMLIKI FOREST VIRUS STUDIES - RNA SYNTHESIS IN INFECTED HAMSTER KIDNEY CELLS

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This is part of a broader project. A summary of this subproject is not available.

67. RNA PROTEIN SYNTHESIS IN INFLUENZA VIRUS-INFECTED CANINE KIDNEY CELLS

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This is part of a broader project. A summary of this subproject is not available.

II. EPIDEMIOLOGICAL STUDIES

A. BLADDER CANCER

68. CANCER INCIDENCE AND MORTALITY IN CANADIAN DIABETICS

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OBJECTIVES: 1) To ascertain the risk factors which may be responsible for differential cancer incidence in diabetics. 2) To further investigate the possible role of saccharin in human bladder carcinogenesis.

APPROACH: A cohort is being assembled, using self-administered questionnaires, from among the 20,000 members of the Canadian Diabetic Association. The questionnaire will contain questions dealing with identifying information, diagnosis and treatment of diabetes, smoking habits, use of artificial sweeteners and dietetic foods and beverages, and a number of other known or suspected risk factors for various cancers. Cancer incidence and mortality in the cohort is being monitored for a period of 10 years using computerized record linkage techniques to link the cohort records with cancer incidence and mortality records maintained by Statistics Canada.

69. ATLANTA CANCER SURVEILLANCE CENTER

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The Atlanta Registry is one of eleven funded and sponsored by the National Cancer Inst. of the United States. Each represents a unique set of persons with respect to climate, race, industrialization, lifestyles, and heritage. Atlanta represents a growing but not particularly industrialized city in the southeastern USA with a large black population and whose longtime resident white population is largely Anglo-Saxon. The study's overall objective is registration and follow-up of every case of cancer in the Atlanta Standard Metropolitan Statistical Area and a separate ten county rural area whose population is largely black. Patients are identified through hospital medical record departments, pathology laboratories, radiotherapy facilities, and death certificates. Collected by specially trained abstractors are demographic information, birthplace, census tract of residence, occupation, use of tobacco and alcohol, site and histological type of malignancy, diagnostic tests and procedures undertaken including surgery, radiotherapy, chemotherapy, and immunotherapy and the name of the physician following the patient. Patients are followed through re-admissions to hospitals, by information from the follow-up physician, and through death certificates. It is hoped that these data will identify persons at unusually high or low risk of cancer through various factors of environment and background. Because the registry is population-based, it will be able to produce incidence data and patterns of diagnostic and therapeutic care for the area. Survival information will be calculated and the effectiveness of different modes of therapy evaluated. Cooperation with special studies such as the relationship of bladder cancer to the use of saccharin and other dietetic or occupational hazards, a study of black women with breast cancer, and the role of antigenic stimulation to multiple myeloma and chronic lymphocytic leukemia is planned.

70. SACCHARIN AND BLADDER CANCER

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It has been suggested from results of some animal studies and one retrospective epidemiologic study that sacchrain use increases the risk of bladder cancer. We felt we could test this hypothesis by studying the changes in the epithelium of the bladder in a large number of autopsies. Saccharin users will be matched for smoking habits and occupational exposures with non-saccharin user controls.

A protocol from sectioning the bladder has been made - about 60 slides will be available from step sections of the bladder. A form for obtaining histories of saccharin use, smoking habits, and occupational and residence histories from relatives has been designed and tested.

Specimens have been collected from a large number of hospitals in upstate New York and in other parts of the country. To date we have collected 582 bladders.

71. EPIDEMIOLOGICAL STUDIES TO INVESTIGATE THE POSSIBLE ASSOCIATION BETWEEN ARTIFICIAL SWEETENERS AND INCREASED RISK OF CANCER

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This investigation is being carried out in five states and four metropolitan areas: New Jersey, Connecticut, Iowa, New Mexico, Utah, Detroit, San Francisco-Oakland, New Orleans, and Atlanta. All but New Jersey are members of the nationwide Surveillance, Epidemiology, and End Results (SEER) network. Inclusion of New Jersey is necessary because of a unique population base and a reporting requirement. New Jersey has the highest bladder cancer mortality rates in the U.S. for males and females.

This study employs a case-control design using incident cases of newly diagnosed histologically confirmed primary carcinoma of the urinary bladder. All cases reside in one of the specified areas. Non-carcinomas are not included, e.g. paraganglioma, melanoma, sarcoma, lymphoma. Malignant papillomas and carcinomas in situ are included. Cancers of other sites in the urinary system are not included. The study population consists of subjects between the ages of 28 and 85 years.

Approximately 3000 cases are enrolled in the study, two-thirds of them 65 years old or older, three-fourths of them males, and most of them white. An additional 800 cases are expected from New Jersey. The control series is a stratified random sample of the general population in each area defined by sex, race (white and non-white) and age (in five year intervals). In each area, twice as many controls as there are cases (6000 from the SEER program and 1600 from New Jersey) were randomly drawn from each stratum.

72. EPIDEMIOLOGICAL INVESTIGATION OF CERTAIN ASPECTS OF HAIR DYE AND SACCHARIN USE AND CANCER RISK

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The saccharin portion of this case-control study was conducted among 302 male and 65 female bladder cancer cases and an equal number of controls matched for age, sex, hospital, and hospital room status. No association was found between use of artificial sweeteners (AS) and diet beverages (DB) and bladder cancer. No dose-response was observed, either with respect to quantity, duration of use, or both. No evidence was found to suggest that AS or DB promoted the tumorigenic effect of tabacco smoking. AS and DB use strongly reflected socioeconomic status among controls with various diagnoses. While our data cannot completely rule out a statistical link between AS and DB use and bladder cancer, the preponderance of epidemiological evidence gathered to date is not consistent with a causal relationship.

In the portion of this program investigating whether an association exists between hair dye use and breast cancer, there have been 292 interviews of breast cancer and control patients completed thus far. This aspect of the grant seeks to determine whether there is a dose-response relationship in terms of frequency of use, duration of use, or cumulative dose; how dye load effects risk; if risk associated with hair dye is different for premenopausal women than postmenopausal women; whether the risk differs in those women believed to be at higher risk due to family history of breast cancer or benign breast disease; and if there is an additional burden placed on hair dye users who dye someone else's hair as well.

73. FDA/NCI STUDY OF THE ROLE OF SACCHARIN IN BLADDER CANCER OF THE GENERAL POPULATION

Narayana, A. S., Culp, D., Child, M. A., Meigs, J. W., Albert, S., Altman, R., Key, C. R., Sullivan, J. W., Austin, R., Thomas, D. B., West, D., University of Iowa, University of Iowa Hospitals

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Following reports suggesting that two artificial sweeteners initiate or promote bladder cancer in animals, cyclamates were banned in the U.S. in 1969, and saccharin was removed from the list of substances 'generally regarded as safe' in 1972. Howe et al. (1977) reported the first positive association between bladder cancer in humans and artificial sweeteners. At present there is not enough evidence to confirm the hypothesis that use of artificial sweeteners increases the risk of bladder cancer in human beings. The study is a collaborative effort of the National Cancer Inst. and nine other areas, and the data pooled consist of information on almost 3,000 newly diagnosed bladder cancer patients over a twelve-month period. All patients between the ages of 21 and 84 years were included in the study, and were interviewed in their homes by specially trained interviewers who also interviewed two age- and sex-matched controls for each case. The number of controls interviewed is approximately 6,000. All the data have been submitted to the National Cancer Inst. for analysis. Samples were used which were large enough to detect even a modest elevation of risk. In addition, the study is based upon a population composed of diverse subgroups, which may distinguish between initiation and promotion of cancer.

74. INTERNATIONAL CASE-CONTROL STUDY OF BLADDER CANCER

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The objectives of this study are: 1. Estimation of relative incidence of lower urinary tract cancer associated with coffee drinking in three areas - Boston, Massachusetts; Manchester, England; and Nagoya, Japan - which vary with respect to exposure rates and ethnic compositon. 2. Estimation of relative incidence associated with drinking other beverages, with smoking, with certain occupational exposures, and use of analgesics and artificial sweeteners. 3. Estimation of relative incidence for each exposure according to histologic type. 4. Estimation of incidence rates and attributable risk measures in each study area.

By home interview, exposure histories will be obtained for about 500 newly diagnosed cases, and an equivalent number of controls, drawn from a geographically defined population, in each study area. Interviewing has been completed in Boston, and will be completed in mid-1979 in both Manchester and Nagoya. Analysis of the Boston data is in progress.

BIBLIOGRAPHIC REFERENCES: Morrison, A.S., Cole, P.: Epidemiology of bladder cancer. In Tannenbaum, M. (ed.): Urologic Pathology: The Bladder. Lea and Febiger, Philadelphia, in press, 1979. Morrison, A.S., Cole, P.: Epidemiology of urologic cancer. In Javadpour N. (ed.): Principles and Management of Urologic Cancer. Williams and Wilkins, Baltimore, in press, 1979.

75. SECOND PRIMARIES POSSIBLY ASSOCIATED WITH CIGARETTE SMOKING

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A series of patients with bladder cancer have been treated using radio-sensitizing methods. Ninety-six percent of the males have a history of cigarette smoking. These patients are followed with special care to determine the frequency of other diseases. Carcinoma of the bronchus has been the most frequent cause of death other than carcinoma of the bladder. The experience of the general population is used for comparison purposes.

76. CANCER OF THE BLADDER IN OPIUM ADDICTS

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The main result of a case-control study of patients with bladder cancer at Shiraz (Pahlavi) University Hospitals was that the risk of developing cancer of the bladder in opium addicts is at least eight times greater than that of the normal population. A prospective study with screening of all opium addicts (by urine cytology for detection of early bladder carcinoma) was thus started at the University. The preliminary results indicate that the risk of developing cancer of the bladder is considerably higher in opium addicts than previously assumed. As of July 1978, 3,500 opium addicts had been screened. The controls, who do not take opium, number 1,750 and are matched by age and sex. A history of smoking habits is obtained. Fourteen histologically confirmed and previously unrecognized cases of bladder cancer have been detected. This early finding indicates that opium addiction should be considered as a carcinogenic agent for cancer of the bladder and further investigation is warranted. Schistosomiasis has not yet been reported in Fars Province and there is little industry.

77. CASE-CONTROL STUDY ON URINARY BLADDER CANCER

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A random sample of 100 persons with urinary bladder cancer, all resident in the Genoa District, reported to the cancer registry is being compared with 200 persons of the same sex and age group affected by different diseases (excluding cancers and other diseases of the respiratory system, cancer of the upper alimentary tract, myocardial infarction, diseases of the urinary system and certain occupational diseases), admitted to the same hospital. Emphasis is placed on occupation and smoking habits. The objective of this study is to uncover possible associations between occupational exposure to chemical carcinogens and urinary bladder cancer.

78. SMOKING AND ALCOHOL CONSUMPTION IN SOME TYPES OF CANCER (CASES AND CONTROLS)

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OBJECTIVE: 1) To prove the hypothesis linking the habit of smoking and the ingestion of alcohol with oral and laryngeal cancers. 2) To determine the risks associated with light and dark tobaccos in relation to certain types of cancer (laryngeal, oral, pulmonary, and bladder). 3) To define the relationship between various smoking habits and cancer. For example, the relationship between reverse smoking (holding the lit end of the cigarette inside the mouth) and oral cancer.

APPROACH: This study will be based on the previous findings obtained by the cancer registry in affiliation with the Social Security. Those findings indicated a disquietingly high incidence of oral and laryngeal cancers in the population studied. This high incidence was offset by low rates of lung cancer.

METHOD: The project is designed to pair off one case and two controls for each type of cancer, that is cancer of the larynx, oral cancer, lung cancer and bladder cancer. One control is matched with the case for age, sex and occupation, whereas the other control is matched for age, sex, socioeconomic class and place of residence.

PROGRESS: To date, 249 cases have been selected, but they have not been matched with controls. In February 1979, a preliminary analysis was performed, and it was determined that a minimum of 60 cases and 120 controls should be obtained for each type of cancer.

The Cancer Registry of the Instituto de Seguros Sociales of Antioquia remains active. An analysis of data for the 10 year period (1968-1967) will soon be published.

79. AMERICAN HEALTH FOUNDATION EPIDEMIOLOGICAL STUDIES

Spritz, N., Wynder, E. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *1st Ave. at E. 24th St., New York, New York,* 10010, United States of America

Tobacco-related cancers and myocardial infarction continue to constitute a major source of death and disability in the U.S. (deaths and morbidity which largely are preventable because of their association to tobacco usage). Collection of data on smoking habits, demographic characteristics, alcohol consumption, occupational and medical histories of patients with tobacco-related diseases and matched controls continues. Annually, 300 lung, esophagus, and bladder cancer patients plus 300 first episode myocardial infarction and 150 pancreatic cancer patients will be interviewed. Results indicate that the risk of developing these diseases increases with quantity smoked, duration of the habit and, for lung and larynx cancer, non-filter

cigarette smoking. Risk of mouth, larynx and esophagus cancer among smokers increases with quantity of alcohol consumed. Increased smoking and low cessation rates are noted among lower socioeconomic groups suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related diseases.

Collection of data (on demographic characteristics, diet and lifestyle habits) in patients with gastrointestinal tract cancer and control patients continues. To date we have 799 gastrointestinal tract cancer cases and an equal number of controls. Fifty percent of the cases have primary colon cancer, 18% have primary rectal cancer, 16% have primary gastric cancer, and 12% have intestinal polyps.

A preliminary analysis of demographic variables and dietary factors has been performed, and a paper is in preparation.

80. EPIDEMIOLOGY OF SMOKING-RELATED DISEASES

Wynder, E. L., Schottenfeld, D., Petrakis, N. L., Bahn, A. K., Bridgers, W., Wood, W., Kuller, L., Spritz, N., American Health Foundation Inc., Dept. of Epidemiology, *320 E. 43rd St., New York, New York,* 10017, United States of America

Although it has been well established that there is an association between smoking and certain diseases, not all smokers develop a tobacco-related disease. Variables such as length of cigarette smoked, depth of inhalation, tar output, carbon monoxide content, etc., along with demographic, occupational and other characteristics modify the exposure and risk for a cohort at a given lifetime exposure to cigarettes. The objectives of this case-control study are to identify individuals or groups at risk of tobacco-related diseases; evaluate environmental, biological and smoking pattern characteristics of persons at high risk and to analyze the relative effects of cigarette modification. Hospitalized patients who meet study criteria are interviewed by trained research interviewers in selected hospitals in New York, Philadelphia, Birmingham, Pittsburgh, Chicago and San Francisco. Cases are persons with a histologically confirmed diagnosis of cancer of the lung, bladder, pancreas, esophagus or oral cavity, or a first myocardial infarction; patients without a tobacco-related disease serve as controls. Two controls for each case, one from the hospital population and one from the residential area of the case, are matched by race, sex and age. Approximately 1,250 cases and 2,500 controls are interviewed each year.

81. EPIDEMIOLOGY OF SMOKING-RELATED DISEASES

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OBJECTIVES: The objectives of this project are to evaluate the risk associated with various smoking habits, including the type of cigarettes smoked, to identify the kinds of cigarettes that may be less carcinogenic to various body organs, and to measure the association between the smoking of various tobacco products and the development of myocardial infarction. This retrospective case-control study uses two sets of controls: One consisting of hospitalized patients and the second consisting of non-institutionalized persons residing in the same neighborhoods of the index cases.

MAJOR FINDINGS: The study continues to demonstrate a dose-response relationship between cigarette smoking and development of cancer of the larynx, lung, oral cavity, esophagus and bladder for both sexes. After adjusting for duration of the smoking habit, inhalation, and butt length, relative risks of developing lung or larynx cancer were consistently lower among long-term smokers of filtered ciagarettes (low tar) than among non-filtered cigarette smokers. For ex-smokers, the risk decreased with increased years of cessation. Risk of mouth cancer for pipe and cigar smokers, who inhaled much less than cigarette smokers, increased with the quantity smoked. Risk of mouth, larynx and esophagus cancer among smokers increased with the quantity of alcohol consumed. More extensive smoking and lower cessation rates were noted among lower socioeconomic groups, suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related diseases.

In accord with the literature, smoking among women is becoming increasingly more prevalent and, contrary to previous reports, persons smoking filtered cigarettes do not appear to significantly increase their levels of consumption once they have changed from a non-filter to a filter cigarette. In addition, when comparing case cohorts, one finds a significant increase in cigarette consumption among young people. Younger cancer patients generally have smoked more cigarettes than older patients. This is consistent with the observation that industry-wide cigarette tar yields have been gradually decreasing over the years, and larger quantities are required to obtain the same risk levels. (Text Abridged.)

82. COMPARATIVE STUDY OF BLADDER CANCER IN THE U.S. AND EGYPT WITH EMPHASIS ON THE ROLE OF SCHISTOSOMIASIS IN CAUSATION OF BLADDER CANCER IN EGYPT

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Cancer of the urinary bladder is one of the few malignant neoplasms in which the role of environmental factors has been determined. At least four of every five cancers in man have their origin in the environment. Bilharziasis is an endemic parasitic disease in Egypt, and affects 40% of all the country's farmers in their third decade of life. Bladder cancer constitutes 28% of all malignant tumors in Egypt. Data were collected from the Ministry of Health in Cairo, Egypt, The Egyptian National Cancer Institute, Cairo, the Department of Urology in Egyptian General and University Hospitals, the Department of Endemic Disease Control, State Health Department and Preventive Medicine and Biostatistics Departments in three Colleges of Medicine, Cairo, Egypt. The incidence of this form of cancer in the western hemisphere and in industries is compared with that in Egypt. Also, case-control studies for Egypt and the U.S. are compared. Histopathological patterns in both sectors will be studied in an effort to find an area of commonality between the types of environmental, social and cultural factors and the patterns of bladder cancer.

83. STUDIES ON THE ASSOCIATION OF SCHISTOSOMIASIS AND MALIGNANCY, WITH PARTICULAR EMPHASIS ON SCHISTOSOMAL POLYPOSIS OF THE COLON

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Schistosomiasis poses an extraordinary threat to military personnel in endemic areas. Infection is easily acquired and results in both early morbidity and the possibility of very long-term service connected illness. The purpose of this study is to investigate the possible association of intestinal schistosomal polyposis and carcinoma of the colon.

OBJECTIVES: (1) To study the available statistics on cancer of the colon in Egypt and its association with Schistosoma mansoni (and polyposis). To take biopsy of polyps at various intervals; to study the incidence of malignancy in patients treated with repetitive courses of niridazole compared to those treated with tartar emetic and untreated patients. (3) Leukocyte typing for determining whether these polyp patients are genetically different from patients with S. Mansoni elsewhere. (4) To study the bladder cancer association to urinary schistosomaisis by blood and urine examination by various immunological testing procedures.

84. A RETROSPECTIVE STUDY OF CANCER IN RELATION TO A SPECIFIC ENVIRONMENTAL FACTOR - WATER NITRATE

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The incidence of testis cancer in Denmark has for years been known to exceed that of neighbouring countries (6.0 new cases/year/100,000 males). In this study a small, geographically limited 'hot-spot', possibly of recent origin, with an incidence of 31.7 new cases/year/100,000 males during the last 2 years (01-06-76 - 01-06-78) has been detected. This particular region differs from the rest of the island of Sjaelland (the island where the capital Copenhagen is situated) in one specific respect: the content of nitrate in deep ground-water supplies. The possibility of the formation of carcinogenic nitrosamines from nitrate, nitrite and secondary amines in humans is being examined. Data are now being collected to determine if there is a significant rise in the incidence of other cancers, particularly bladder cancer.

85. COMPARE OCCURRENCE AND LEVELS OF DRINKING WATER CONSTITUENTS AMONG 12 MATCHED PAIRS OF HIGH AND LOW CANCER MORTALITY COUNTIES (ABBREV)

Greathouse, D. G., Michael, G., Kraemer, D., U.S. Environmental Protection Agency, Office of Research & Development, Health Effects Research Lab., *5555 Ridge Ave., Cincinnati, Ohio,* 45268, United States of America

OBJECTIVE: The aim of this project is to determine if matched counties with contrasting cancer mortality rates use drinking water that differs significantly in terms of occurrence and levels of contaminants, treatment technologies used, and/or source type (ground or surface).

APPROACH: Twelve pairs of matched counties were selected; matching criteria were region of the country, avg. educational level, percent of the population employed in the manufacturing industry, percent urbanization, total population years at risk. Within each pair, one county had a high and the other a low mortality rate for females due to colon, rectum, bladder, and liver cancer. Historical water quality and treatment information were collected for performance. Extensive water analyses were performed; analysis included determinations for 40 inorganics, trihalomethanes, TOC, fluorescence, asbestos, radionuclides, and mutagens.

PROGRESS: The field work has been completed and all water samples have been analyzed. Most of the data has been computerized. It is anticipated that the data analysis effort will begin by October 1, 1979 and be completed by March 31, 1980.

86. CANCER AND DRINKING WATER QUALITY IN NORTH CAROLINA

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In this study 3,000 cancer cases and an equal number of frequency matched non-cancer controls were compared on several aspects of drinking water quality. Sites examined were colon, rectum and bladder; matching criteria were age, race, sex and geophysical region. Data sources were state mortality, and state and regional water supply statistics. The water systems were characterized on the basis of source, type of chlorination, and presence of upstream pollution (previous use) for the 1960 time period. Urban residence, occupation and socio-economic status are also being controlled in the analysis. Preliminary results show small and significant odds ratios for all three sites (especially bladder and rectum) for treatment, source, and previous use.

87. EPIDEMIOLOGIC STUDY OF BLADDER CANCER RISK ASSOCIATED WITH TRIHALOMETHANES IN DRINKING WATER

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OBJECTIVE: To assess the bladder cancer risks associated with exposure to purgeable organics in drinking water.

APPROACH: Include exposure to purgeable organics as one of the risk factors to be evaluated as part of the large National Cancer Institute supported study of bladder cancer and saccharine usage.

PROGRESS: All of the cases and controls have been interviewed, much of the historical water supply and water quality data has been abstracted, and the water sampling and analysis effort is well underway.

88. RELATIONSHIP OF ORGANIC CONTAMINANTS IN DRINKING WATER TO CANCER MORTALITY AND MORBIDITY IN CONNECTICUT

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OBJECTIVE: This study will provide the necessary data on drinking water supplies in Connecticut to determine the relationship between (1) type of water supply and drinking water cancer and mortality over time and (2) organics in drinking water and the incidence of bladder cancer.

APPROACH: This objective will be accomplished through two studies: (1) Drinking water and cancer mortality - This study will utilize existing drinking water data for the state of Connecticut along with newly collected data for comparison with the tumor registry. (2) Bladder cancer study - This study is part of a large scale EPA bladder cancer study. It will be a case-control study using 540 cases and 1080 controls selected in Connecticut. Questionnaires will be given and water samples will be collected for chemical analysis.

89. RELATIONSHIP BETWEEN BRACKEN INFESTATION AND CANCER MORTALITY IN VICTORIA, AUSTRALIA

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Rural Victoria has areas of bracken fern infestation. The mortality from all types of cancer is being compared between the populations living in bracken and non-bracken areas. Prior epidemiological and experimental research has indicated an increased risk of bladder cancer and bowel cancer in association with the ingestion of bracken fern.

90. TRI-COUNTY STUDY OF CANCER OF THE MOUTH, ESOPHAGUS, LARYNX, STOMACH, COLON, RECTUM, LUNG AND BLADDER

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PROJECT OBJECTIVES: (1) To study the epidemiology of cancer of the gastrointestinal tract, lung and bladder, and (2) to study the possible relationship between dietary factors and cancer at the aforementioned sites.

PLAN AND METHODS: We are attempting to interview all patients in Erie, Niagara and Monroe Counties who develop histologically confirmed neoplasms of the gastrointestinal tract, lung and bladder. Fifteen patients at the Veterans Administration Medical Center have been entered in the study since the last report.

The major emphasis in the interview is on dietary habits. Questions are asked about time and frequency of eating meals, types and amounts of food eaten, and methods of food storage and preparation. In addition, questions are asked about alcohol consumption and use of tobacco. Certain data such as age, occupation and marital status are gathered.

In addition to interviewing cases, we are also interviewing neighborhood controls matched on age (plus or minus 5 yrs.) and sex.

FINDINGS, RESULTS: We have not undertaken any definitive analyses of our data since the numbers at various sites are still too small. We have, however, completed a methodological study based on this series which examines degree of agreement between case-spouse and control-spouse pairs with regard to food frequency. We presented our findings on this at the meeting of the Society for Epidemiologic Research on June 14, 1979.

91. A MORTALITY STUDY OF PEST CONTROL OFFICERS

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A pilot study is being conducted to examine the feasibility of obtaining information from local authorities in England and Wales on pest officers employed from 1946 onwards, and on the pesticides used. A special interest is being taken in the use of 'antu' (alpha-naphthylthiourea), a rodenticide which chemical tests suggested could be associated with bladder cancer, and which was generally withdrawn from use in the UK in 1967. Commercial pest control firms are also being contacted and some may cooperate in a retrospective study; the feasibility and value of prospective studies will also be considered.

92. ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN THE ETIOLOGY OF HUMAN BLADDER CANCER

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To study the association between occupation, dietary and social patterns and bladder cancer, 348 bladder cancer patients

(248 males, 100 females) and 2 controls per case (matched by sex, age within 5 years, and geographical location) were interviewed. Information was obtained about occupation (including contact with fourteen classifications of industrial chemicals), family background, past illnesses, analgesic intake, beverage consumption, smoking habits. The data are being analyzed.

93. INDUSTRIAL EMISSION IN NEW JERSEY AND ITS RELATIONSHIP TO CANCER

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The NCI has a contract with the New Jersey Department of Health to investigate bladder cancer. This ongoing investigation has identified specific places in New Jersey where bladder cancer rates are elevated, and are continuing to increase. The EPA has developed expertise in taking environmental samples (e.g., air, water, soil, etc.) and analyzing them for known or suspected carcinogens. The NCI will inform the EPA concerning the specific places in New Jersey where environmental sampling needs to be done. The EPA will collect samples, and provide these data to the NCI.

94. THE CYTOLOGICAL DIAGNOSIS OF BLADDER TUMORS IN DYESTUFF WORKERS

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The production and use of benzidine and beta-naphthylamine in the dye industry of Japan were prohibited by law in 1971. However, there are still 4,037 workmen (including retired men) who have been exposed to carcinogenic amines, and risk developing a bladder tumor in the future. This study aims to perform continuous follow-up urine examination of the workers. For the early detection of bladder tumors, routine cystoscopy was considered to be quite unsuitable. The Papanicolaou smear technique of urine examination was introduced into the dye industry of Japan in 1961. A total of 4,037 men were screened first by wet smear and then by Papanicolaou smear. During the 22 years from 1955 to 1977, 192 cases of occupational bladder tumor were discovered; 15 out of 108 men with positive Papanicolaou smears have shown no tumors on cystoscopy; 7 men with negative Papanicolaou smears showed bladder tumors on cystoscopy (false negative); 47 out of 137 men with suspicious Papanicolaou smears had bladder tumors. Seventeen specimens obtained from the occupational bladder tumor patients were histopathologically examined. Of these 17 specimens, 8 showed papillary cancer type, 6 showed an inverted proliferating tumor, and 3 were carcinoma in situ. This study continues.

95. BLADDER CANCER MORTALITY IN HUDDERSFIELD, YORKSHIRE

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Huddersfield is a center for the manufacture of dyestuffs, and cases of occupational bladder cancer have occurred. This study will assess the impact of occupational cases on male bladder cancer death rates in the whole town and in subdivisions since the 1930s and will assess whether the town's raised male death rates can be attributed solely to past exposure in dyestuff manufacture and will check whether bladder cancer mortaity among women is normal.

96. IMMUNOLOGICAL CRITERIA IN THE DETECTION OF HIGH OCCUPATIONAL CANCER RISK AMONG TEXTILE WORKERS

Korosteleva, T. A., Belokhvostova, A. T., Movsesjan, K. S., Kuznetsov, S. I., N.N. Petrov Research Inst. of Oncology, Laboratory of Experimental & Clinical Oncoimmunology, *Leningradskaya St. 68, Leningrad 188646, Union of Soviet Soc. Republics*

The purpose is to examine textile workers handling direct dyes containing benzidine and beta-naphthylamine. The workers have been divided into 3 groups according to extent and duration of exposure. The following immunological tests have been used: (1) determination of benzidine as haptene in the blood serum of workers, splitting of the direct dyes by specific rabbit immune serum; (2) determination of an endogenous carcinogen, the metabolite of tryptophane-3-hydroxyanthranilic acid (3HAA), using specific rabbit immune serum in immune diffusion in agarose as a criterion of disturbances in tryptophane metabolism. Such disturbances have frequently been observed in patients with cancer of the urinary bladder and some other sites (breast, lung); (3) determination of the index of phagocytic activity of blood neutrophils as related to specific and non-specific factors. Particles of activated carbon, loaded by benzidine- and 3-HAA -azoproteins, were used as specific factors, and staphylococcus aureus as a non-specific factor; (4) determination of blast transformation of peripheral leucocytes to PHA and benzidine- and 3-HAA-azoproteins. The blood of non-exposed workers and healthy donors was used as a control.

97. CANCER EDUCATION AND SCREENING PROGRAM FOR TEXTILE AND FURNITURE INDUSTURIES

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The first project, the Cannon Mills Cancer Education and Screening Program in Kannapolis and Concord, North Carolina was completed in 1977, while other industries are presently participating in similar programs. One of the objectives is to detect specific industrial cancer risks in the textile and furniture industries (e.g., bladder cancer, lung cancer, nose cancer). So far, none of these cancers have shown any appreciable accummulation, i.e., the risk of developing these cancer types appears no higher in the two industries compared to the general population of North Carolina. A description of the first completed project follows: A cancer education and screening program was conducted among 19,000 Cannon Mills workers in North Carolina. Lectures were presented on company time for all employees within each of the three 8-hour shifts. This group education contained information on six cancer types felt to be amenable to screening and in which early detection can be expected to increase survival: breast, cervix, colon, bladder, prostate and oral cavity. After the completion of lectures employees were offered a screening examination. Thirteen thousand employees accepted and were screened between 2/1/76 and 1/31/78. The cost of screening was ten dollars per person.

Thirty-two asymptomatic patients who participated in the screening were discovered to have cancer. The compliance among those who had positive findings, and who were advised to see their M.D.'s was 90% among female and 81% among male employees.

The program received unanimous approval of the Carbarrus County Medical Society, which has recommended it for other counties. The state of North Carolina has also adoptedthis program as a pilot program among 10,000 state employees, with the assistance of Blue Cross/Blue Shield.

98. BLADDER CANCER AND THE PRINTING INDUSTRY - AN HISTORICAL PROSPECTIVE MORTALITY STUDY OF THE PRINTING INDUSTRY

Leon, D., Beral, V., University of London, London School of Hygiene & Tropical Medicine, Dept. of Epidemiology, *Gower St., London WC1E 7HT, England, United Kingdom*

OBJECTIVE: To investigate whether print workers have an increased risk of dying from cancer of various sites, especially bladder cancer, compared to members of the general population.

APPROACH: The study is of a prospective kind. Approximately 7-9000 print workers who were employed in the industry in a variety of occupations between 1949 and 1963 are being identified from the membership records of two printing trade unions. It will then be ascertained, with the assistance of the Office of Population Censuses and Surveys, whether any of them have since died and if so their cause and date of death.

Sex, date of birth, details of occupation on entry into the union, major occupation changes subsequent to entry while remaining in the union, duration and period of union and branch membership, firm on entry into branch and other relevant information is also being collected from union records. On the basis of this information the risks of dying from various causes within the different occupational groups will be examined and compared. Duration of 'exposure', measured in terms of length of full membership, will also be examined in relation to risk, to see if any dose-response type relationships can be established.

If a significantly increased risk is found for cancer of the bladder, or any other site, the analysis of the deaths from that cause may be extended by carrying out a case-control study.

This would allow a more detailed examination of the relationship between type and duration of exposure to risk.

99. MORTALITY AND INDUSTRIAL HYGIENE STUDY OF THE PRINTING TRADES

Boeniger, M., Stern, F., Nicholson, W., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio*, 45226, United States of America

Published literature on the printing trades suggests that a significant number of health hazards exist. Workers are exposed to a variety of substances, i.e., carbon black, oil mist, polychlorinated biphenyls, polyvinyl chloride, carbon disulphide. A number of unusual health conditions observed in earlier studies have been suggested by researchers. These are cancers of the skin, lung, bronchial cavity, digestive system, and bladder. Other suspected diseases include increased heart disease, acro-osteolysis, and cirrhosis of the liver. A detailed characterization, including industrial hygiene assessment of the industry and a retrospective study of the mortality patterns among selected specialists within the printing trades industry, is being conducted. The contractor, Mt. Sinai Hospital, New York City, has performed walk-through industrial hygiene studies in selected printing establishments. Records from a printing union local have been collected and are being analyzed.

NIOSH is extending its study of the printing industry to the point of purchase segment of the screen printing trades. In-depth industrial hygiene characterization of this trade will be performed in the New York metropolitan area. All work in this latter study will be conducted by NIOSH industrial hygienists.

100. URINARY CYTOLOGICAL INVESTIGATIONS FOR DETECTION OF BLADDER CANCER AMONG RUBBER WORKERS EXPOSED TO PHENYL-2-NAPHTHYLAMINE

Herivan, R. M., Ministry of Chemical Industry, Labour Protection & Hygiene Centre, Cytology Laboratory, *59 Pop de Basesti, 73244 Bucharest 3, Romania*

The objective is to monitor the incidence of urinary bladder cancer in subjects exposed to phenyl-2-naphthylamine in the rubber industry. Cytological exfoliative screening with Giemsa stain and Papanicolaou's classification is used for early detection.

101. RUBBER AND CABLE MAKING STUDY

Duncan, K. P., Employment Medical Advisory Service, *Chepstow Pl., London W2, England, United Kingdom*

OBJECTIVES: To monitor the incidence of bladder cancer in subjects who enter the industry after known carcinogens have been removed and also to monitor the general cancer incidence.

102. CANCER INCIDENCE AND MORTALITY AMONG RAILROAD WORKERS

Howe, G. R., Lindsay, J., Miller, A. B., University of Toronto, *Medical Sciences Bldg., Toronto, Ontario*, M5S 1A8, Canada

In a recent case-control study (Tobacco Use, Occupation, Coffee, Various Nutrients, and Bladder Cancer, G.R. Howe et al. JNCI, in press) an association was observed between any occupation related to railroads and increased risk of bladder cancer. The present study is a cohort study using pension records from a large Canadian railroad company. Records from 1965 onwards are being linked using computerized techniques, to the Canadian mortality data base, and records for those from 1969 on are being linked to the Canadian cancer incidence reporting system. Thus mortality between 1965 and 1976, and cancer incidence between 1969 and 1976 can be related to various occupations within the railroad industry.

103. CANCER INCIDENCE AND MORTALITY IN A COHORT OF RAILWAY EMPLOYEES

Howe, G. R., Miller, A. B., University of Toronto, Epidemiology Unit, *Medical Sciences Bldg., Toronto, Ontario*, M5S 1A8, Canada

OBJECTIVE: The study is designed to evaluate increased risk of cancer, particularly bladder cancer, in a cohort of railway employees classified by their occupation at time of retirement. This is a follow-up to an observation made in a previously reported case/control study of bladder cancer where increased risk was associated with exposure to fumes in railway workers.

APPROACH: Ex-employees of the Canadian National Railway alive at January 1, 1960 and who received a pension from the CNR form the cohort. The fact and data of death are on record and cause of death will be established using computerized record linkage to the national mortality data maintained by Statistics Canada. Cancer incidence amongst those alive as of January 1, 1969 will be determined using similar techniques with respect to the national cancer registry data (Statistics Canada). Comparisons will be made between those individuals whose occupations involve exposure to fumes and those whose occupations did not and also with Canadian population data.

PROGRESS: The basic records have been computerized and are currently ready for the linkage process.

104. MORTALITY AND INDUSTRIAL HYGIENE STUDY OF LEATHER INDUSTRY WORKERS - NCI

Stern, F., Brown, Fajen, J., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio*, 45226, United States of America

Several case-control studies have indicated that individuals employed in the leather industry may experience an excess risk of developing bladder cancer. Cole, in a case-control study, found that leather workers had a relative risk of 2 for developing bladder cancer when compared with a group of matched controls. Another case-control study conducted on all bladder cancer cases, referred to the Roswell Memorial Park Research Institute, found a relative risk for bladder cancer of 12.94 for persons employed at least 5 years in the leather industry.

In an attempt to gain additional insight into the relationship between bladder cancer and the leather and leather products industry, mortality rates for bladder cancer were examined in those U.S. countries where the leather industry comprised at least 5 percent of the total employment of the country. Twenty-four counties in six states met these criteria. A definite pattern of increased bladder cancer was found in the 'leather counties' in New England and New York State, however, no unusual risks were found in the 'leather counties' of Pennsylvania and Tennessee. It should be noted that the leather industry in Pennsylvania and Tennessee consisted mostly of small-scale operations of the shoemaker-repairer trade, whereas the leather industry in New York and New England was mainly leather tanneries.

Leathermakers are potentially exposed to chromates, benzidine-based azo dyes and numerous other suspect carcinogens. In addition, NIOSH has recently detected environmental levels of dimethylnitrosamine in a leather tannery. Dimethylnitrosamine has been demonstrated to be an extremely potent carcinogen in numerous animal studies.

A cohort mortality/industrial hygiene study will be conducted to further evaluate the above mentioned excess risk data. The first phase of the investigation will be a feasibility study to determine the extent of exposure, to characterize the work environment and to assess the feasibility of conducting the mortality portion of the study.

105. SPATIAL AND TEMPORAL VARIATIONS IN FOUR COMMON CANCERS IN BLACK GOLD MINERS FROM SOUTHERN AFRICA

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In previous work on the gold miners, the pattern of cancer in Black gold miners over the eight-year period 1964-71, constituting 2,926,461 man-years of employment, was studied. Of the 1,344 cancers found, primary liver cancer accounted for 52.8%, oesophageal cancer 12.1%, cancer of the respiratory system 5.4%, and cancer of the bladder 4.8%. Analysis of the spatial distribution of these four cancers, both on subcontinental and local scale, showed distinct gradients of significantly higher and lower incidence than expected. In the case of primary liver cancer in Mozambique and oesophageal cancer in Transkei, the spatial distribution reflects closely that found in the general resident population of each territory. The crude incidence rate of primary liver cancer in gold miners from Mozambique

dropped sharply over the period of the survey. The survey continues.

106. BLADDER CANCER, LEUKEMIA AND LYMPHOMA AMONG NEW YORK AND WISCONSIN DAIRY FARMERS - A DEATH CERTIFICATE STUDY

Blair, A. E., Cantor, K., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

A few studies have suggested that dairy farmers have elevated mortality from bladder cancer, leukemia, and lymphoma. To evaluate this lead, 300 deaths from each neoplasm in heavy dairying counties in New York and Wisconsin were individually matched to one control (dying of some other disease) of the same age, race, sex, year of death and county of residence. Type of farming operation for case and control farmers will be determined using records from the State Cooperative Extension Service. The proportions of death certificates listing farmer as the usual occupation and the type of farming operation will be compared in the cases and controls.

107. BLADDER CANCER MORTALITY IN CERTAIN AREAS AND INDUSTRIES

Davies, J. M., Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton, Surrey SM2 5PX, England, United Kingdom*

A number of towns have been selected, most of which are important centers for industries suspected of giving rise to a bladder cancer risk. As a first step male and female bladder cancer mortality rates in these towns over some 25 years will be compared with national and regional rates. As a second step a total of some 3,000 death certificates of male residents dying with bladder cancer ('cases') will be matched with 'control' death certificates of male residents dying from other causes at the same ages and dates; the occupations of cases and controls will be compared, using the occupations recorded on the death certificates.

108. AGE-TIME-COHORT ANALYSES OF MORTALITY

Barrett, J. C., University of London, London School of Hygiene & Tropical Medicine, Dept. of Medical Statistics & Epidemiology, *Keppel St., London WC1E 7HT, England, United Kingdom*

This method of mortality analysis was first described in J. Hygiene (Camb.) 71, 253-59, 1973. It consists of the simultaneous use of age, time and cohort factors. Of the three factors, age at death, epoch of death and epoch of birth, one seems almost superfluous. It is nevertheless worthwhile to include all three, allowing for the constraints that the redundancy imposes. This procedure is being applied to published data for England and Wales on breast cancer, bladder cancer and prostate cancer mortality, 1951-1970.

109. MORTALITY STATISTICS

Hansluwka, H. E., Krastev, R., Bachmann, R., Heller, B., World Health Org., Division of Health Statistics, *1221 Ave. Appia, Geneva 27, Switzerland*

Statistical data concerning mortality following the 'A' list of the International Classification of Diseases are collected on a world-wide basis, processed, stored and published annually (Volume 1 of the World Health Statistics Annual). Data on cancer mortality according to the four-digit list of ICD are collected and stored in WHO's data bank. Epidemiological and statistical analyses of cancer mortality are periodically published as a special subject in the World Health Statistics Quarterly (WHSQ), e.g., Breast, WHSQ, No. 6, 1975; Uterus, WHSQ, No. 8, 1975; Digestive Organs and Peritoneum, WHSQ, No. 3, 1976: Hodgkin's Disease, WHSQ, No. 2, 1977: Lung, WHSQ, No. 2, 1977: Pancreas, liver, ovary, cancer survival statistics, WHSQ, No. 1, 1978; cancer of eye, cancer mortality in Europe, 1970-74, WHSQ, No. 2, 1978; Sex differentials in cancer mortality and morbidity, WHSQ, No. 4, 1978; Cancer of the Urinary Bladder, Kidney and Skin, WHSQ, No. 1, 1980; Social and Economic Implications of Cancer in the United States of America, WHSQ, No. 1, 1980, as well as Cancer Statistics, Report of a WHO/IARC Expert Committee, Techn. Rep. Ser. 632, 1979.

110. AGE-EFFECTS AND TEMPORAL TRENDS IN CANCER

Moolgavkar, S., Stevens, R. G., Lee, J. A., Inst. for Cancer Research, Fox Chase Cancer Center, *7701 Burholme Ave., Philadelphia, Pennsylvania*, 19111, United States of America

Multifactorial analysis of cancer incidence and mortality data can shed light on the dynamics of temporal evolution of the disease, and permits the extraction of statistically adjusted age-specific incidence curves that are free of the distorting effects of temporal trends thus increasing the precision with which pathogenetic models for carcinogenesis can be tested against incidence data. In the present study a multifactorial analysis of incidence and mortality data for cancer of the bronchus, bladder, pancreas and the large bowel, and malignant melanoma will be made. Data will be obtained from various populations, and analyzed to study the relative importance of early and late environments on the temporal trends in these cancers. Good data on cigarette smoking are available in the U.K. and U.S.A. This information will be incorporated into the analyses to study the association between cigarette smoking and carcinomas of the lung, bladder, and pancreas in these countries. It will then be possible to adjust for the effects of cigarette smoking in these diseases in order to study more subtle trends. The statistically adjusted age-specific incidence curves will be used to test a two-stage model for carcinogenesis in a separate study.

111. EPIDEMIOLOGIC INVESTIGATION AND CASE-CONTROL STUDIES OF BLADDER CANCER PATIENTS

Fokkens, W., Rotterdamsch Radiotherapeutisch Instituut, Dept. of Documentation & Epidemiology, *Groene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

All bladder cancer patients treated at the Rotterdam Radiotherapy Institute are interviewed about their occupational history and about other suspect factors such as smoking and phenacetin use. Since March 1977, in collaboration with Health Insurance Unions, interviews are also conducted on bladder cancer patients under 60 years of age living outside the Rotterdam region.

112. INCIDENCE OF CANCER AMONG SELECTED GROUPS IN DENMARK

Clemmesen, J., Sorensen, B. L., Finseninstitutet, Danish Cancer Registry, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

A series of studies of cancer risk in selected groups and occupations is being undertaken. These will include the distribution of cancer among hairdressers, and risk of thyroid cancer among patients with thyroid struma, the geographical distribution of leukaemia and Hodgkin's disease in Denmark and a case-control study of cancer of the bladder.

113. EPIDEMIOLOGICAL FACTORS IN URINARY BLADDER CANCER

Vahlensieck, W. E., Adolphs, H. D., University Hospital of Urology, *Venusberg, 5300 Bonn, Nordrhein Westfalen, Federal Republic of Germany*

Information is being collected from patients with urinary bladder cancer on occupational exposure to carcinogenic factors, eating habits with particular reference to saccharin and cyclamate, tobacco and alcohol consumption, drug abuse and metabolic disorders.

114. BLADDER CANCER - CASE-CONTROL STUDY OF OCCUPATION AND OTHER RISK FACTORS

Connolly, J. G., Chapman, J. W., University of Toronto, Dept. of Urology, *Medical Sciences Bldg., Toronto, Ontario*, M5S 1A8, Canada

OBJECTIVE: To study the association between occupation, dietary practices, medical background and personal habits and bladder cancer.

APPROACH: 348 bladder cancer patients (248 male, 100 female) and 2 controls per case matched by sex, age within 5 years and residence were interviewed.

PROGRESS: Univariate results completed for all variables. Multivariate logistic regression analyses performed for occupations, and hypotheses formulated to explain excess of bladder cancer in occupations in high risk category.

115. URINARY BLADDER CANCER AND OCCUPATION IN LYON

Dubernard, J. M., Centre National de la Recherche Scientifique, Centre d'Epidemiologie, *8 ave. Rockefeller, LP No. 005440 c/o Fac. Med., 69008 Lyon, France*

In a case-control study all cases of urinary bladder tumors in three hospitals in the city of Lyon are being registered and a questionnaire on occupational factors and toxic products used administered. Two controls for each case, one a patient without the disease and one population control, are used.

116. LONG-TERM EFFECTS OF THE HEALTH STATE OF OCCUPATIONAL EXPOSURES TO CHEMICALS

Maties, R., Muica, N., Ghise, O., Tanase, T., Modorcea, V., Sabau, P., Horvath, P., Academia de Stiinte Medicale, Inst. of Hygiene & Public Health, Dept. of Occupational Medicine, *Strada Biserica Amzei 29, Bucharest, Romania*

Malignant tumors as well as cardiovascular and obstructive lung diseases may be caused by occupational exposure to various chemicals. The aims of the project are (1) to develop a suitable epidemiological methodology; (2) to analyze accurately the long-term effects of occupational exposure to chemicals, and (3) to determine the specific patterns of morbidity and mortality from malignant tumors in workers formerly exposed to chromium salts, asbestos and aromatic amines. The project includes a study of mortality from lung cancer, pleural mesothelioma and bladder cancer over the last 20 years in workers exposed to various chemicals, compared to the mortality recorded in the general population of the area, and a morbidity study based on the result of periodic medical examinations performed annually among workers at risk.

117. MEDICAL SURVEILLANCE AND INTERVENTION - BLADDER CANCER

Bayliss, D. L., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluation & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

As aromatic amines, specifically beta-naphthylamine, benzidine, and di-chloro-benzidine, have been responsible for cancer of the bladder in up to 100 percent of workers, the continued and increasing use of such carcinogens, not only in dye and pigment production but also in pharmaceuticals, detergents, food colors and specialized chemicals, makes it imperative that surveillance should continue so that situations similar to the current bladder cancer epidemic in New Jersey be prevented. A cooperative agreement is being developed with the National Cancer Institute to place all such exposed workers under medical surveillance. This will include periodic examinations and constant follow-up to detect early changes consistent with the development of bladder cancer.

118. PROPORTIONAL OCCUPATIONAL ANALYSIS USING DEATH CERTIFICATE DATA

Marrett, L. D., Meigs, J. W., Connecticut Cancer Epidemiology Unit, Dept. of Epidemiology & Public Health, *30 College St., New Haven, Connecticut,* 06510, United States of America

Occupational data for a random sample of 8,000 Connecticut adults who died between 1959 and 1961 have been collected and coded. Occupation, industry, birthplace and cause of death for this general population sample will be compared with those of deceased Connecticut Tumor Registry incidence cancer cases. Such analyses will control for sex, age at death, and socioeconomic status. These data are currently being used in the studies of occupational factors in urinary bladder cancer and chronic leukaemia in Connecticut. It is hoped that the results of these and similar studies on other cancer sites will suggest new hypotheses regarding associations between occupational exposures and subsequent cancer experience.

119. IDENTIFICATION OF OCCUPATIONAL GROUPS AT HIGH RISK OF CANCER

Kennedy, J., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Surveillance, Hazard Evaluation & Field Studies Division, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

Activities listed below are contracted out to the Johns Hopkins University, Dr. Irving I. Kessler, Principal Investigator, and have been carried out since June 1975.

The purpose of this project is to identify high-risk occupational groups in terms of incidence of certain rare cancer sites. The analysis would make it possible to identify potentially dangerous occupational exposures. The results obtained from two independent analyses will allow examination and re-analysis of most data sets in terms of morbidity (cancer) from dangerous occupations or industries newly identified.

From an existing data base containing lifetime occupational information on: a) 800 patients divided into 2 equal groups (persons with cancer of the urinary bladder and persons with other diseases -excluding cancer of any kind); b) a group of more than 1,800 patients (one-half with one of several neoplasms); and c) a group of 1,392 patients (one-half with Parkinson's Disease and the other half without this condition); high-risk occupational groups will be identified in the disease groups.

During FY 77, Dr. Kessler, Principal Investigator, presented some results on the bladder cancer patients to the Surveillance Branch and other interested persons in NIOSH. At the time of the presentation, improvements and refinements to the research by the addition of input from industrial hygienists were suggested that would allow NIOSH to gain the greatest benefits. A modification and extension of the contract has been proposed for incorporation into this project for FY 78 and FY 79.

FY 78 ACCOMPLISHMENTS: Project continuing as planned. Anticipate delays due to Principal Investigator changing his primary affiliation from Johns Hopkins to University of Maryland.

120. CASE-CONTROL STUDY OF CANCER OF THE URINARY TRACT IN THE PROVINCE OF TURIN, ITALY

Terracini, B., Vineis, P., Zanetti, R., Costa, G., Universita degli Studi di Torino, Istituto di Anatomia e Istologia Patologica, *Via Santena 7, 110126 Turin, Italy*

The age-adjusted incidence rate of bladder cancer (including papillomas) in men living in the city of Turin around 1970 was 21.2 per 100.00 person-years while the corresponding rate for the rest of the Province is 10.8. The absolute number of cases per year is on the order of 120 in the city and 70 in the rest of the Province. A case-control study has been undertaken in order to collect information on smoking experience, alcohol and coffee drinking habits, previous use of artificial sweetners, social class and occupational history throughout life. The latter refers to both occupation titles and the industry in which employed. Social class is estimated based on present or last occupation as well as number of years at school and ratio between number of people living in the family unit and number of rooms. Only residents in the Province are interviewed. The survey is being conducted in three of the eight urological hospital departments of the Province of Turin and only hospital based controls are used. It is planned to extend the study to all urological hospital departments operating in the Province and to add population-based controls for residents in the city of Turin. Preliminary results on 75 cases-hospital control pairs have been submitted for publication.

121. CANCER INCIDENCE IN FIVE CONTINENTS - VOLUME IV

Muir, C. S., Waterhouse, J. A., Powell, J., Shanmugaratnam, K., Centre International de Recherche sur le Cancer, Unit of Epidemiology & Biostatistics, *150 Cours Albert Thomas, 69372 Lyon Cedex 2, France*

The fourth volume in this series is in preparation and will be published in 1981. In addition to incidence data obtained from some 88 registries, covering the period 1973-1977, studies on distribution of histological types of bladder and thyroid cancer and Hodgkin's disease and on urban and rural incidence differentials will be included.

122. A CASE-CONTROL STUDY OF ETIOLOGICAL FACTORS IN URINARY BLADDER CANCER IN A RURAL PART OF DENMARK

Mommsen, S., Sell, A., Wolf, H., University Hospital of Aarhus, Dept. of Oncology, *Norrebrogade 44, DK8000 Aarhus C, Denmark*

Epidemiological data are collected in 210 consecutive, newly diagnosed patients with bladder cancer. The patients are interviewed about exposure to chemical materials; alcohol, tobacco, medication and coffee consumption; use of artificial sweeteners; history of illnesses particularly of the urinary system and delay. Controls are selected randomly from the general population, matched to cases by sex, age and residence on a one-to-one basis for the males and on a one-to-two basis for the females. The possible interrelationship of the variables with other epidemiological variables is studied. These include socio-economic factors, urban factors and occupational exposure. The data are coded for statistical analysis.

In addition, the N-acetyltransferase phenotype is studied in patients and controls, smokers and non-smokers in a rural population and the results are compared with results for an urban population.

123. CASE-CONTROL STUDY IN COPENHAGEN OF URINARY BLADDER TUMORS

Clemmesen, J., Jensen, O. M., Finseninstitutet, Danish Cancer Registry, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

The aim is to undertake a case-control investigation of factors associated with lower urinary tract cancers in Copenhagen (bladder, renal pelvis, ureter, urethra). The following factors will be investigated: tobacco smoking, diet, with particular regard to intake of coffee and artificial sweeteners, use of drugs, in particular analgesics, and occupation. Qualitative and quantitative exposure among newly diagnosed cases (500) will be compared with two independent age-matched and sex-matched control groups drawn from among hospital patients (500) and the total population (1,000), respectively.

124. EPIDEMIOLOGICAL STUDY OF BLADDER CANCER

Miller, A. B., Hill, G. B., Steele, R., University of Toronto, *Medical Sciences Bldg., Toronto, Ontario,* M5S 1A8, Canada

A recent case-control study of the epidemiology of bladder cancer conducted by the NCIC Epidemiology Unit produced a number of important findings. The current study's objective is to re-evaluate these findings in a second case-control study conducted in different geographical areas in Canada. Areas where occupational causes may be more important, the roles of tobacco, particularly the differential effect of filter and regular cigarettes, artificial sweeteners, instant and regular coffee in males as well as females, hair dyes, and the association with non-public water supplies will be studied. The study is population-based with case and control acquisition from the whole of Alberta and from southern Ontario including the areas of metropolitan Toronto, Kingston, Windsor, London, and Hamilton. All newly diagnosed cases of bladder cancer in the areas included in the study are being identified. An equal number of age- and sex-matched controls will be obtained from population registries. All cases and controls are interviewed in their own homes with a questionnaire similar to that utilized in the first study.

125. EPIDEMIOLOGY OF BLADDER CANCER IN WEST YORKSHIRE

Cartwright, R. A., Yorkshire Regional Cancer Org., *Leeds LS16 6QB, Yorkshire, England, United Kingdom*

Yorkshire has one of the highest mortality rates in the United Kingdom for bladder cancer with an SMR for males in 1969-73 of 114. Incidence and mortality are unevenly distributed within the area and the aim of the project is to account for the high mortality and the variation in incidence. The study is a case-control investigation of prevalent and incident cases for certain hospital areas within the Yorkshire area, including Bradford and Kirklees. The controls are neighbourhood and hospital in type. A questionnaire has been constructed which explores personal habits, past medical history and occupational history in depth. Details of the natural history of the bladder cancer are also recorded. The first phase of the study, dealing with prevalent cases, will be complete in 1979, whilst the incidence study will continue for some years beyond that date. It is hoped that at least 600 cases will be interviewed in the first phase of the study.

126. EPIDEMIOLOGIC INVESTIGATION OF PATIENTS WITH CARCINOMA OF THE BLADDER

Fokkens, W., Rotterdamsch Radiotherapeutisch Instituut, Dept. of Epidemiology, *Groene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

OBJECTIVE: Tracing carcinogenic factors or circumstances in the past of patients with bladder tumors (and, incidentally, other cancers).

APPROACH: Collecting and analyzing data about former professions; occupational histories; special factors: rubber, dyes; drugs, e.g., phenacetine; and smoking habits.

PROGRESS: The investigations led to the identification of three populations at risk, which were screened for cytological tumor detection in urine samples. To date 3 cases have been found in an early stage (out of about 340 men). An unsuspected hazard was identified in Graphic Industry. There is an indication that phenacetine abuses can initiate bladder tumors. Up until now this study has been limited to bladder cancer patients, treated in the Rotterdamsch Radio-Therapeutisch Institute. For the past year this project has also included the investigation of bladder cancer patients under the age of 60, outside the Rotterdam region. The motive for the extension of this study was the experience that the majority of all occupational bladder cancers become manifest under the age of 60. These patients are traced by the departments of sickness-insurance of the trade unions in the Netherlands. Our experience over the last year indicates that in a very high percentage of these relatively young patients the initiation of their bladder cancer must be ascribed to occupational circumstances. The investigation for this category of patients is planned for a period of 4 years.

127. EPIDEMIOLOGICAL STUDY OF BLADDER CANCER

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In Japan, the age-adjusted mortality rate for bladder cancer has levelled off in males and there is a possible downward trend for females over the last two decades. These trends were observed despite the recent remarkable increases in potentially hazardous environmental agents. In addition, the proportion of bladder cancer and kidney cancer deaths has been constant, 7:3, over these 20 years. These findings are very suggestive of the aetiological importance of host factors in bladder cancer production. Host factors and several environmental factors are now being investigated accordingly in Metropolitan Nagoya by a case-control study. Along with this investigation, familial cases are compared with non-familial cases in respect to tryptophan metabolism, HL-A types and others. Geographic clusters of bladder cancer deaths by city and county have been tested by a newly developed significance test, based on a Monte Carlo method. The test revealed no significant clusters of either high or low bladder cancer mortality in Japan from 1969-1971.

128. EPIDEMIOLOGY OF BLADDER CANCER IN ISRAEL

Bertini, B., Beemer, A. M., Cuttin, E. S., Health Inst., Epidemiological & Cytological Research Unit, *P.O. Box 16320, Tel Aviv, Israel*

The relationship between urinary lithiasis, very frequent in Israel, and urinary tract cancer is being studied in 850 patients. Duration of the bleeding and degree of inflammation until appearance of the tumor are analyzed.

129. EPIDEMIOLOGICAL STUDIES OF CANCER IN LOUISIANA

Gottlieb, M. S., Pickle, L., Blot, W. J., Tulane University of Louisiana, School of Medicine, Dept. of Medicine, *1430 Tulane Ave., New Orleans, Louisiana,* 70112, United States of America

Death certificates for cancer of the lung, nasopharynx, pancreas and bladder will be identified for selected Louisiana parishes for the years 1960-1975. Controls will be matched by parish of residence, year of death, age (within 2 years), sex and race. The frequency of occurrence of names attributable to groups with a common heritage will also be compared, as will relationship of residence at death and distance from selected industries, and water source. The objective is to determine single or multiple factors which can be identified as associated with a greater risk in cases compared with controls. This will form the basis of subsequent additional observational studies.

Sub-studies on populations exposed to unique substances are included.

130. CANCER EPIDEMIOLOGY AND PREVENTION RESEARCH CENTER

MacMahon, B., Miettinen, O., Yen, S., Hutchison, G., Morrison, A., Gutensohn, N., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The Cancer Epidemiology and Prevention Research Center supports a broad program of studies investigating the etiology of the major human cancers, with the ultimate objective of developing knowledge which will lead to the prevention of these diseases. Focus in research includes: cancer of the breast, especially in relation to patterns of metabolism of endogenous estrogens in young adult life, oral contraceptive use, and other hormonal factors. Hodgkin's disease is another major component of the program with emphasis on the roles of environmental exposure and person-to-person transmission. Other studies include cancer of the pancreas, multiple myeloma, bladder cancer, and methodology, including life table analysis of survival data and various aspects of significance testing and interval estimation.

Using a variety of resources, the studies employ different epidemiologic approaches including case-control studies, prospective cohort studies, and review of existing data in the Department. Many of these studies are developed on the basis of studies designed and completed in earlier grant years. Some studies are supported for a planning phase only while others are continuations of ongoing data collection analysis.

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131. INTERNATIONAL CASE-CONTROL STUDY OF BLADDER CANCER

Morrison, A. S., Cole, P. T., Aoki, K. O., Ohno, Y. N., Obata, K. S., Leck, I., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The objectives of this study are: (1) To estimate the risk ratio and attributable risk of developing lower urinary tract cancer (bladder cancer) associated with coffee drinking in geographic areas which vary with respect to exposure rates and ethnic composition; (2) to estimate the risk ratio and attributable risk of bladder cancer associated with drinking other beverages, smoking, participating in certain occupations, use of analgesics, and ingestion of artificial sweeteners and bracken fern. In Boston (Massachusetts), Manchester (United Kingdom) and Nagoya (Japan), all new cases of bladder cancer in geographically defined populations were ascertained over two to three year periods. Controls were selected from the general population. Exposure information was collected by home interview. Analysis of the data is in progress.

132. FACULTY RESEARCH AWARD (APPLICATION)

Morrison, A. S., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

This is a proposal for a five-year program of research in cancer epidemiology. Projects are planned in three areas: etiology, screening, and natural history. In the area of etiology, studies will be made of cancer of the breast and cancer of the urinary bladder. Studies of breast cancer will focus on a) the relationship of breast parenchymal pattern to both breast cancer risk factors and incidence, and b) the hormonal correlates of parenchymal pattern. For bladder cancer, a detailed analysis will be made of the relationship of incidence to occupational hazards. The work on screening will involve development of basic methods in the areas of program evaluation (especially of late outcomes), cost-efficiency, and characteristics of screen-detected cancer. The last topic includes measurement of lead time, length bias, and the timing of metastasis formation in relation to the time of diagnosis by screening. The studies of natural history involve two approaches. The first will be a 'descriptive' evaluation of rates of metastasis formation for several common cancers. The second approach will be the analysis of the development of metastases in relation to incidence risk factors, for primary cancers of the breast and bladder.

133. BLADDER CANCER RISK FACTORS IN UTAH

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Previous epidemiological studies have identified several risk factors in the etiology of bladder cancer and a national study has been completed recently to determine whether these factors are associated with the disease. This was a case-control study of incidence cases in defined geographic areas and randomly selected population controls. Utah participated in this 12-month study, but the number of cases identified in Utah in 12 months (127) will not allow adequate sample size to perform the multivariate analysis techniques needed to test several important hypotheses. Since coffee and tobacco comsumption are low in the Utah population, hypotheses concerning these risk factors can be studied without the problems found in other populations where the groups of non-users are small. In particular, coffee can easily be studied in Utah, as well as caffeine and the interaction of both with tobacco in the etiology of bladder cancer. Urban-rural differences and an increasing incidence for older males have also been noted in the state and identification of risk factors for these findings may suggest new hypotheses. The proposed plan will utilize the same design as used in the national study, but collect more data on coffee consumption. This will be done for two years and a year will be necessary for data analysis.

134. BLADDER CANCER IN NEW HAMPSHIRE, VERMONT, AND MAINE

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New Hampshire, Vermont, and Maine have high rates of bladder cancer for both males and females. Since bladder cancer is usually more common in males than females, conducting a study in these three states provides an unusual opportunity to study bladder cancer in both sexes.

The study will be restricted to those areas within the three states which have high rates of bladder cancer for either males or females. The study will include a next-of-kin survey for all deaths due to bladder cancer in the past five years in those counties and a newly diagnosed case survey covering a period of twenty-four months. One control will also be selected for each case in both the next-of-kin survey and the new incidence survey. In addition to the surveys, a library study to characterize industrial and other relevant features of the study areas will be performed, as will be a collection of air and water quality samples. The study will be patterned on the Special Study of the Role of Saccharin in Bladder Cancer.

The primary objective of the study is to assess whether there is an association between certain environmental exposures and the high rates of bladder cancer in New Hampshire, Vermont, and Maine. In addition, the study will help to refine the understanding of associations that are already known to exist.

The exposures being investigated are: 1) Consumption of artificial sweeteners 2) use of tobacco products, 3) occupational exposures, 4) residential history (for source of drinking water and air quality), 5) consumption of coffee and other beverages, 6) certain illnesses and medical therapies, 7) use of hair dyes.

Of particular interest among these exposures are occupational exposures and air and water quality. In order to provide additional data to help analyze any associations, a historical study of industry in the data will be done and air and water quality samples will be taken in certain areas.

135. STUDIES OF CANCER-PRONE FAMILIES

Blattner, W. A., Greene, M. H., Tucker, M. A., Mann, D., Goldin, L., Goedert, J., Blayney, D., Fraser, M. C., Bartch, J., Zener, K., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Environmental Epidemiology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The purpose of this project is to conduct and coordinate interdisciplinary studies on cancer-prone families in order to clarify the role of genetic mechanisms and host-environmental

interactions in carcinogenesis. Clinical studies of high-risk families have suggested etiologic relationships between cancers, constellations of which may cluster in individuals (multiple primary neopiasms) or may be scattered over the family tree (familial neoplastic syndromes). Discovery of laboratory test abnormalities in certain cancer-prone families, such as subclinical immune dysfunction in family members predisposed to lymphoma, melanoma, and some gastrointestinal malignancies, immunogenetic determinants in acute leukemia, Hodgkin's disease, and Waldenstrom's macroglobulinemia, DNA repair defects in leukemia and other familial neoplasm syndromes, metabolic defects in bladder cancer-prone families, and clinically apparent premalignant conditions in individuals prone to colon cancer and melanoma, have provided insights into the mechanisms of susceptibility to cancer.

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136. PILOT STUDY ON THE NATURAL HISTORY OF BLADDER PAPILLOMAS

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A major dilemma in urological practice today is the inability of physicians to predict which benign appearing bladder papillomata will eventually invade and which will not. An epidemiological study has been undertaken to investigate this problem. A sample of Baltimore area urologists are participating in an investigation of all their patients recently diagnosed as having bladder papillomas or early stage carcinomas. The biopsy and other tissue specimens are being analyzed in detail by Dr. Joseph C. Eggleston. Their urological and medical records are being reviewed and all patients are being interviewed with respect to known and potential bladder carcinogen exposure. It is hoped that this study will it possible to correlate the histological characteristics and exposure histories of the bladder tumor patients with their subsequent clinical course. At this time, 22 or 9.1% of 243 papilloma patients have been found to develop bladder carcinoma after precursor papillomas. These appear more likely to be smokers, and to have histories of certain environmental exposures than do other papilloma cases. The papillary lesions associated with subsequent malignant transformation are not readily distinguished from others. The data are now being analyzed with respect to: (1) the incidence and prevalence of bladder papillomas in the Baltimore area; (2) the incidence or probability of developing bladder and other cancer according to host and lesion characteristics; (3) the survival experience of papilloma patients, and (4) the multivariate predictor, based on host factors and papillary lesion characteristics, for events following papillomas.

137. CASE-CONTROL STUDY USING S.S.A. IDENTIFICATIONS

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This study presents a new methodologic approach to linking disease in a geographic area to an occupational etiology. Examples include bladder cancer in New Jersey and leukemia or brain tumors in east Texas. The Social Security Administration records the employer, for each contributor, for each quarter. For any individual, reconstruction of a continuous employer history is feasible.

We propose first to ascertain cases of a particular disease, such as bladder cancer in New Jersey and controls, consisting of New Jersey citizens of like age, race, and sex with other causes of death. SSA would then provide continuous work histories for cases and controls. Specific employers or categories of employers represented in excess among cases as compared to controls may then be identified. These industries or employers would then be subject to in-depth cohort mortality studies. The cohort mortality study may identify new etiologies for the disease in question or identify continuing exposures to known carcinogens.

138. TEMPORAL EVOLUTION OF CANCER

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We propose to apply multifactorial methods incorporating epidemiological parameters to the analysis of cancer incidence and mortality data. The goals of this research are to study the relative importance of early and late environments on the temporal evolution of cancers of specific sites, to relate this evolution to environmental factors when possible, and to adjust for temporal trends in order to extract age-specific incidence curves that are free of the distortions produced by historical effects. Such an analysis is important to the epidemiologist seeking to understand the dynamics of the temporal evolution of cancer, and to the cancer biologist seeking to test models for the pathogenesis of cancer against incidence data.

We propose to study the following tumors in various populations: (a) Carcinoma of the Lung; (b) Carcinoma of the Bladder; (c) Carcinoma of the Pancreas; (d) Malignant Melanoma; (e) Carcinoma of the Large Bowel. Specifically this research will use incidence and mortality data to study: (1) The association between cigarette smoking and carcinomas of the lung, bladder, and pancreas; (2) The importance of oral contraceptives in malignant melanoma; (3) The dynamics of the temporal evolution of, and the 'true' effects of age on, all the tumors listed above.

B. WILMS' TUMOR

139. EPIDEMIOLOGY OF CHILDHOOD MALIGNANCIES IN JAPAN

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Patterns of occurrence of childhood malignancies in Japan are being studied in relation to selected risk factors based on data from nationwide registration. A total of 10,575 children (5,951 males; 4,624 females) under age 15 were registered 1969-1977. Malignancies included 4,607 leukemia, 750 malignant lymphoma, 1,002 neuroblastoma, 485 Wilms' tumor, 230 liver tumor, 892 retinoblastoma. Age-specific incidence rates were calculated for each. When compared with vital statistics figures for all Japan, maternal ages had little or no influence, but significant risk elevation was noted under age three with increase in weight at birth, for leukemia, neuroblastoma, Wilms' tumor, testis tumor, and teratoma. Abdominal radiation exposure during the latter part of pregnancy was noted to enhance leukemia risk when compared with 1,011 controls of similar age. Down's syndrome was frequent in leukemia under age three and many cases of congenital malformation including seven hemihypertrophy, five aniridia, six congenital heart disease, were recorded co-existent with Wilm's tumor. The mean ages for retinoblastoma were five, six and seventeen months for bilateral, unilateral with family history, and unilateral without family history cases respectively. Analysis continues.

140. DELETION OF (IIP) AS A CAUSE OF WILMS' TUMOR

Riccardi, V. M., Strong, L., Ferrell, R., Harberg, F. J., Boniuk, M., Hittner, H. M., Holmquist, G. P., Baylor College of Medicine, School of Medicine, Dept. of Medicine, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

We intend to study genetic aspects of Wilms' tumor, a common childhood cancer, and some of its associated clinical features. We will do this by analyzing the peripheral blood leucocyte chromosomes of previously identified patients with Wilms' tumor and/or aniridia in order to determine whether interstitial IIp deletions account for more instances of these abnormalities than previously suspected. Approximately 120 Wilms' tumor patients from the Texas Medical Center (TMC), including the M.D. Anderson Hospital (MDAH) are available to us, as are 25 patients with aniridia. We will also karyotype tumor cells from patients with de novo or recurrent Wilms' tumors that come to surgery. Leukocyte and tumor chromo-

some analyses will utilize G-banding techniques coupled with amethopterin synchronization to obtain maximally elongated prophase or prometaphase chromosomes. In addition, electrophoretic assays of red blood cell lactic dehydrogenase A activities will be performed to look for deletions of that enzyme's structural gene locus. We have already shown that locus to be near the IIp13 region, which, if deleted, leads to the aniridia-Wilms' tumor association.

141. OHIO CENTRAL DATA BASE FOR CHILDHOOD CANCER

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The objective is to provide baseline information on demographic patterns for cancer morbidity and mortality in Ohio children. This includes case-finding information regarding type of cancer by age, race, sex, place of residence, staging at initial diagnosis and institution of initial diagnosis. Abstracts are being prepared on hospital discharge of all newly diagnosed children with cancer beginning January 1975 from all the major treatment centers for children in Ohio. These abstracts utilize forms currently in use in a broader data collection program, the Children's Hospital Automated Medical Program (CHAMP), a medical research computer center located in Children's Hospital, Columbus, Ohio. In addition, an epidemiological questionnaire to be completed by parents is also being collected. This includes general questions on family history, including cancer in relatives and malformations, with additional specific information on patients with leukemia, brain tumors, Wilms' tumor and malignant lymphoma.

142. GENETIC STRUCTURE AND FUNCTION OF HUMAN CHROMOSOME II

Housman, D. E., Gusella, J., Massachusetts Inst. of Technology, Center for Cancer Research, Dept. of Biology, *77 Massachusetts Ave., Cambridge, Massachusetts*, 02139, United States of America

We propose to use recombinant DNA techniques to isolate DNA sequences located on human chromosome 11. These DNA sequences will be localized to specific regions of the chromosome by a deletion mapping procedure in which cloned DNA segments will be hybridized to DNA isolated from hybrid cell lines carrying deletions of various lengths of the short arm of chromosome 11. The DNA sequences isolated by this procedure will be used in a number of studies in which the genetics of chromosome 11 play an important role. These include: 1. Mapping of deletions of 11p which are associated with aniridia and Wilms tumor. 2. Identification of sites in the DNA of chromosome 11 which exhibit polymorphism with respect to sensitivity to restriction endonuclease digestion. These sites will then be used as markers in two types of studies: a. Diagnosis of thalassemia and hemoglobinopathies by analysis of linked markers. b. Determination of the possible linkage of familial aniridia to the 11p13 chromosomal segment. 3. A long-range objective of this proposal will be to use the DNA probes isolated in this study to analyze in detail the structure and function of specific regions of chromosome 11.

143. PROGRAM PROJECT IN CLINICAL GENETICS

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Work in the Wisconsin Clinical Genetics Center (WCGC) includes: 1) Delineation of new birth defect syndromes, their cause, natural history, prognosis and treatment; 2) study of 'known' birth defects to better delineate their phenotypic spectrum, pathogenesis and cause, and the means to detect carriers, and to detect affected individuals prenatally; 3) cytogenetic studies of new and known aneuploidy syndromes; 4) studies of genetic pleiotropy in man; 5) investigations of the nature of gene expression in tissues, organs and cells of individuals (expressivity), in individuals vis-a-vis their genotype (penetrance), and in generations vs. their genotypes (phenotrance), in skeletal dysplasias (achondroplasia, hypochondroplasia), malformation syndromes (Wiedemann-Beckwith syndrome, prune belly syndrome, etc.), and cancers (retinoblastoma, Wilms' tumor, carotid body tumors, multiple glomus tumors and multiple cutaneous leiomyomata; 6) studies of methods of numerical taxonomy in clinical studies and genetic nosology; 7) studies of prenatal diagnosis, the incidence of Down's syndrome and neural tube defects in Wisconsin; 8) studies of the prevalence of developmental disabilities in Burnett Co. and Dane Co. Wis.; 9) health and genealogical surveys of all of the Old Order Amish in Wis., Illinois, Iowa, Missouri and Minnesota; 10) total dissections of fetuses and infants with known (genetic) syndromes and experimental studies of pathogenesis of congenital malformations in aneuploid mice; 11) causal, nosological and empiric recurrence risk studies in severe MR -especially that associated with primary CNS malformations; 12) mutational and genetic analysis of the experimentally (EMS) induced phenomenon of unstable premutation in Drosophila; 13) interdisciplinary studies of phenotype, pathogenesis, cause, nosology and recurrence risk in skeletal dysplasias and human intersexuality; 14) studies of the effects on offspring of parental consanguinity in Wis. rural Catholics; 15) studies on the pathology, anatomy and genetic defects of aborted fetuses and stillborn infants; 16) studies of mucopolysaccharide metabolism and of lysosomal hydrolases in human mucopolysaccharidoses, mucolipidoses, and lipidoses; 17) biochemical, EM, and histochemical studies of many pigment mutations in mouse, mink, and man.

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144. GENETICS OF EMBRYONAL TUMORS

Strong, L. C., Riccardi, V. M., Ferrell, R., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Pediatrics/Biology, *c/o Texas Medical Ctr., 6723 Bertner Ave., Houston, Texas*, 77030, United States of America

The objective of this study is to identify specific genes or chromosomal segments which may be involved in the etiology of embryonal tumors. Patients referred to the M.D. Anderson Hospital with childhood cancer and family history of childhood cancer, congenital anomalies, developmental delay, or multiple primary tumors, are candidates for study. It is anticipated that some 20 patients will be studied each year. Peripheral lymphocytes and, when present, tumours are reviewed for chromosomal aberrations detectable by metaphase and prometaphase banded (Giemsa, R. banding, etc.) preparations and/or by polymorphic biochemical markers. The frequency of 11p in about 100 patients with Wilms' tumor will be assessed.

C. OTHER RENAL AND UROLOGICAL SYSTEM NEOPLASMS

145. RELATION BETWEEN ENVIRONMENT AND CANCER

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OBJECTIVE: The objective of the research project is to study the relation between different factors in the general and working environment and the presence of cancer in exposed populations. Attempts will be made to relate individual factors as well as environmental exposures to the development of a particular tumor form.

APPROACH: The Swedish National Mortality Registry and the Swedish Cancer Registry are used in the study. With the aid of recorded deaths or registered cases of cancer, the geographical distribution in the country is studied. At sites where accumulations are found, case-related studies are performed to evaluate environmental factors. Studies are also made in specific counties where an increase of a particular tumor form has been suspected or in communities where the presence of local industries has been related to the presence of specific tumors, either in the working population or in the general environment.

PROGRESS: An observed increase in the incidence of liver cancer was found to be related to an increase of autopsy frequency. A higher incidence was found in large cities in Sweden, which could be related to alcohol habits, also demonstrating themselves as an increase in the cases of liver cirrhosis.

In a Swedish county a population density gradient was found for lung cancer. As air pollution levels are low, the difference was attributed to differences in smoking habits between rural and urban areas. The cancer increase in one community was related to the handling of asbestos in an industry.

Continued work in the project involves an analysis of the geographical distribution of pancreas and kidney cancer followed by a study on cancer in children in the age groups up to 10 years.

146. CASE-CONTROL STUDY OF CANCER DEATHS IN ILLINOIS COUNTIES SERVED BY 1 N CHLORINATED AND NON-CHLORINATED GROUND WATER

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There is concern among many scientists that chlorination of drinking water may be related to cancer of the gastrointestinal and urinary tract. Chloroform is only one of the many potential carcinogens that have been identified in chlorinated drinking water increasing the concentration of halogenated compounds. This case-control study investigates whether or not an increased human risk of gastrointestinal and urinary tract cancer can be found in communities using chlorinated ground water in comparison to those communities using non-chlorinated ground water. Two hundred and seventy-two chlorinated and 270 non-chlorinated communities were identified. The total 1970 population size of the chlorinated and non-chlorinated communities was 704,867 and 415,561 respectively. All deaths of males and females attributed to cancer of the gastrointestinal and urinary tract and matched control deaths for the identified communities were extracted from Illinois Death Certificate Tapes for the period 1973-1976. Cases consisted of the oesophagus, stomach, large intestine, rectum and rectosigmoid junction, liver and intrahepatic bile ducts specified as primary, gallbladder and bile ducts, pancreas, kidney, urinary bladder and other unspecified urinary organs as classified by the Eighth Revision of the International Classification of Diseases. Controls for the study were selected from a pool of non-cancer deaths. Such factors as age, sex, urban versus rural residency, and standard metropolitan statistical area (SMSA) versus non-SMSA residency were controlled for this study.

147. EPIDEMIOLOGICAL STUDIES OF THE RELATIONSHIP BETWEEN RE-USE OF WATER AND HAZARDS TO HEALTH

Beresford, S. A., Ives, K. J., Packham, R., University of London, Royal Free Hospital School of Medicine, Dept. of Clinical Epidemiology & Social Medicine, *21 Pond St., London NW3 2PN, England, United Kingdom*

The aim of the studies is to investigate the effects on the health of populations drinking water derived from water sources contaminated with domestic and industrial waste, with particular reference to cancer of the digestive system, and of the genitourinary system. The first stage of the studies is to examine the association between cancer mortality and the source of water supply in terms of the history of pollution and degree of re-use. The hypothesised association arises mainly from the Mississippi River study although other studies have also examined this association. Possible disease outcomes other than cancer will also be investigated to provide a basis for formulating further hypotheses.

148. CASE-CONTROL STUDY OF GASTROINTESTINAL AND URINARY TRACT CANCER MORTALITY IN RELATION TO DRINKING WATER CHLORINATION

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Based on previous research which indicated that females residing in areas with chlorinated water had higher risks of dying of gastrointestinal and urinary tract cancer than their counterparts receiving non-chlorinated water, a case-control mortality record study has been initiated in 19 stable New York counties, to see if gastrointestinal and urinary tract cancer mortality can be related to urban or rural residence, mean income, population density, raw water quality, pH, nitrate concentration and color of the water provided for consumption.

149. RENAL PELVIS AND URETER CANCERS

Wynder, E. L., American Health Foundation Inc., *320 E. 43rd St., New York, New York*, 10017, United States of America

This is part of a broader project. A summary of this subproject is not available.

150. KIDNEY CANCER AND TOBACCO CONSUMPTION

Vutuc, C., Kunze, M., Flamm, J., Universitat Wien, Inst. of Hygiene, Social Medicine & Epidemiology, Arbeitsgruppe fur Sozialmedizin und Epidemiologie, *Kinderspitalgasse 15, 1095 Vienna, Austria*

The aim of this retrospective survey is to determine if smoking causes kidney cancer. The emphasis will be on cancers of the renal pelvis - about 150 such cases will be studied - although cancers of the renal parenchyma will also be included. For each case two matched controls with non-tobacco selected disease will be interviewed. The results of tobacco smoking in both cases and controls will be compared with data from the Austrian population collected in 1972 and 1977.

151. THE RELATIONSHIP OF ANALGESIC CONSUMPTION TO CANCER OF THE KIDNEY AND URINARY TRACT IN N.S.W.

Stewart, J. H., Ford, J. M., Rainsford, F., Taylor, S., Kanematsu Memorial Inst., *Macquarie St., Sydney, N.S.W. 2000, Australia*

OBJECTIVE: The objectives of this investigation are to prove that heavy consumption of analgesics is responsible for the excessive frequency of renal pelvic carcinoma in New South Wales, and to identify the drugs or derivatives which are responsible.

APPROACH: Two parallel lines of investigation are being pursued; 1) a laboratory project testing analgesic drugs and their metabolic derivatives for carcinogenicity when implanted into the bladders of mice; 2) an epidemiological survey to determine which analgesic substances are associated with the development of renal pelvic cancer.

152. CARCINOMAS OF THE URINARY TRACT AND ASSOCIATION WITH ANALGESIC ABUSE

Duggin, G., Horvath, J. S., Tiller, D. J., Royal Prince Alfred Hospital, Renal Unit, *Missenden Rd., Camperdown, Sydney, N.S.W. 2050, Australia*

The aim of the study is to determine the incidence of carcinomas of the urinary tract in patients who abuse analgesics, particularly those containing aspirin, phenacetin, caffeine, paracetamol and salicylamide. Patients studied will be those referred to Royal Prince Alfred Hospital with analgesic-induced renal disease (analgesic nephropathy) or those patients known to abuse analgesics. This group of patients will be followed prospectively to determine the frequency and type of carcinomas of the urinary tract and which analgesic is specifically associated with the development of these carcinomas. It is anticipated that between 50 and 400 such persons will be followed. Controls will be age- and sex-matched patients with comparable renal disease, who do not consume analgesics, attending the same clinic.

153. THE CARCINOGENICITY FOR TRANSITIONAL EPITHELIUM OF METABOLITES OF PHENACETIN

Stewart, J. H., Ford, J. M., Westmead Hospital, Dept. of Medicine, *Westmead, N.S.W. 2145, Australia*

The aim of this epidemiological survey is to determine whether there is an association between heavy analgesic consumption, in particular of phenacetin-containing preparations, and the occurrence of transitional-cell carcinoma of the renal pelvis or ureter in New South Wales. The association between analgesic abuse, renal papillary necrosis and carcinoma of the renal pelvis has been recognized sufficiently often, especially in Sweden, to suggest either that some component of analgesic powders and tablets is carcinogenic for uroepithelium, or that tissue destruction and inflammation associated with papillary necrosis in some way predisposes to the development of cancer. In New South Wales, Taylor has calculated an incidence of carcinoma of the renal pelvis nine times greater in kidneys damaged by analgesics than in those with non-analgesic inflammatory disease. At Sydney Hospital 35 per cent of cancers of

the kidney and upper urinary tract seen between 1970 and 1976 were transitional-cell carcinomata, and 48 per cent of these occurred in analgesic habitues. The following methods will be used: (1) All patients aged 15 years and over reported to the New South Wales Central Cancer Registry with cancer of the kidney and upper urinary tract (ICD Codes 189.0, 189.0, 189.1 and 189.2) and females with bladder cancer (ICD Code 188.9) will be included. The study group will be divided into two, the first comprising those with transitional-cell carcinoma of the renal pelvis ureter or bladder, and the second those with renal cell carcinoma, with which analgesic consumption has not been implicated. (2) An appropriately matched (i.e. for age, sex and socio-economic status) group of control subjects will be drawn from the community using an accepted method. (3) A questionnaire covering possible occupational exposure to urinary carcinogens, smoking habits, analgesic intake and previous urinary tract disease, will be completed at interview and the data obtained coded for computer analysis.

154. EPIDEMIOLOGY OF CANCER OF THE RENAL PELVIS AND URETER

Ross, R. K., Henderson, B. E., Yu, M., Gerkins, V. R., University of Southern California, School of Medicine, Dept. of Community & Family Medicine, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

The proposed research is a continuation of a case-control study of the epidemiology of cancer of the renal pelvis and ureter in Los Angeles County. The study is designed to test for multiple antecedent risk factors or these diseases with special emphasis on prior heavy analgesic consumption, occupational exposures, cigarette smoking, and coffee consumption. The study is in year 2 of a proposed five-year program. The final case group will consist of 200 cases of carcinoma of the renal pelvis and ureter identified by the Los Angeles County/USC Cancer Surveillance Program. Controls are neighborhood controls individually matched to the cases by date of birth (plus or minus 5 years), sex, and race.

Data are obtained by telephone interviews conducted by a trained nurse epidemiologist with questionnaire information focusing on the above items. The study will evaluate the relative importance of each of these suspected risk factors in disease development and, for analgesic usage, the specific analgesic component responsible for increased risk.

155. KIDNEY TUMORS - INFLUENCE OF DIETARY FACTORS (RATS)

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This is part of a broader project. A summary of this subproject is not available.

156. APPLIED TOXICOLOGY OF UNSATURATED CHLORINATED HYDROCARBON CONTAMINANTS FOUND IN VARIOUS NAVAL OPERATIONAL ENVIRONMENTS

Andersen, M. E., Jenkins, L. J., U.S. Dept. of Defense, Navy, Naval Medical Research Inst., Toxicology Detachment, *Wright Patterson A.F.B., Dayton, Ohio,* 45433, United States of America

The toxic properties of the unsaturated halogenated hydrocarbons and other materials found in naval operational environments have been described on a phenomenological level. The objective of this work unit is to investigate in depth the mechanisms by which the toxicity of these chemicals is expressed. Only from such detailed studies can data be developed that will allow the establishment of reasonable, accurate and defensible guidelines for control of toxic environments.

1,1-Dichloroethylene (1,1-DCE), identified as a trace contaminant in submarine atmospheres, causes liver damage in rats and is suspected of causing cancer in mice. The toxic effects of 1,1-DCE on the liver and kidney and its metabolism will be studied in rodents. The role of metabolism in producing a toxic intermediate from 1,1-DCE will be examined and the factors controlling the production and subsequent inactivation of toxic intermediates will be investigated in rats exposed to low, atmospheric concentrations of 1,1-DCE. Data obtained in these studies will be used to defend suggested limits for exposures to 1,1-DCE.

157. MORTALITY RISK STUDY OF COPPER SMELTER WORKERS

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The study aims to determine if there exists an excess risk of mortality due to certain diseases, especially lung, renal or prostate cancer, among copper smelter workers. These workers are exposed to lead, arsenic, cadmium and sulphur dioxide. Five levels of exposure to these different contaminants have been determined: (1) no exposure; (2) exposure to concentrations always below the threshold limit values (TLV) accepted by the National Inst. of Occupational Safety and Health (US); (3) average exposure below TLV but with possible incursion over; (4) average exposure always over TLV; (5) exposure known but never measured. Employees who have worked at least one year for the company between 1 January 1952 and 31 December 1957 are followed up to 31 December 1977. In all 2,246 workers will be studied. The risk of mortality related to different cancers will be evaluated by comparing the number of cancers observed in a cohort to the number expected in a population of the same age and sex, for each year, in the Province of Quebec.

158. MORTALITY, MEDICAL, AND REPRODUCTIVE STUDY OF LEAD WORKERS

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MORTALITY STUDY OF LEAD WORKERS: Lead phosphate administered subcutaneously to rats has resulted in the induction of renal tumors. Renal tumors in rats have also been induced by lead acetate-containing diet. Lead oxide appears to act synergistically with benzo(a)pyrene in pulmonary tumorigenesis in Syrian hamsters, since lead is reportedly cumulative in the lung. Workers in lead smelters and battery plants may breathe or ingest lead as a result of poor work hygiene practices. Possible carcinogenic or co-carcinogenic effect deserves examination. Although the authors of a study concerning carcinogenesis among lead battery plant workers concluded that their results do not support a specific cancer risk, the data indicate that such a risk may be present. In order to further assess the possible excess cancer risk related to lead exposure, a further retrospective cohort study is planned on workers exposed to lead and its compounds. A contract for establishing a master file and doing follow-up was given to Westat, Inc. The cohort has been identified and follow-up is underway.

REPRODUCTIVE STUDIES: Since as early as the mid 1800s, the effects of lead exposure on human reproduction have been observed. In 1860, Constantin Paul collected case histories on the reproductive effects in both wives and male lead workers and in women workers who have had exposure to lead. Recently, Lancranjan et al, (1975), in a study of 150 male lead battery plant workers found that those in groups strongly affected by lead exposure had 'decreased fertility due to anthenospermia (reduced viability of sperm), hypospermia (both reduced numbers), or teratospermia (malformed), frequently associated.' All these reports suggest effects of lead or reproduction through both male and female exposure. Two reproductive history studies are being done, one to examine the effects on the male, and one to examine the effects on the female worker. Most of the data for the study of male workers have been collected, coded, and prepared for analysis. The study population for the study of effects of lead exposure on women workers has not yet been selected. Due to external delays, and due to limited personnel at NIOSH, this study will be postponed one year. (Text Abridged.)

159. MORTALITY STUDY OF LEAD WORKERS

Selevan, S. G., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluation & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

Lead phosphate administered subcutaneously to rats has resulted in the induction of renal tumors and renal tumors have

also been induced in rats by lead acetate-containing diets. Lead oxide appears to act synergistically with benzo(a)pyrene in pulmonary tumorigenesis in Syrian hamsters; lead is reportedly cumulative in the lung. Workers in lead smelters and battery plants breathe or ingest lead as a result of poor hygiene. Possible carcinogenic or co-carcinogenic effect deserves examination. Although the authors of a study on cancer among lead battery plant workers concluded that their results do not support a specific cancer risk, the data suggest that such a risk may be present. In order to further assess the possible excess cancer risk to lead exposure, a further retrospective cohort study is planned on workers exposed to lead and its compounds.

160. EPIDEMIOLOGIC STUDY OF WORKERS IN PETROLEUM REFINERIES AND PETROCHEMICAL PLANTS

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An NCI study examined the cause-specific mortality experience of workers who were active members of Oil, Chemical and Atomic Workers International Union (OCAW) Locals in Texas at the time of death. Proportional mortality ratios (PMR's) for stomach and brain cancers, for leukemia, and for multiple myeloma were elevated among white males who worked in petroleum refineries and petrochemical plants and were Union members for at least 10 years. In particular, increased relative frequencies of stomach and brain cancer deaths were found among white male members who were employed at a refinery in Port Arthur (Plant A). In addition, PMR's were elevated for lung cancer among non-whites and stomach cancer in both racial groups employed at another refinery in Port Arthur (Plant B).

Observed numbers of deaths from leukemia, and from cancers of the kidney and skin were greater than expected among white males at Plant B, but observed numbers were very small.

A third refinery in Beaumont, Texas, was found to have excessive frequencies of lung and brain cancers among workers. A case-control study will be done as a timely second step to examine excess deaths from certain cancers in greater detail.

Detailed work histories will be obtained from each case and control to determine length of employment in these plants, specific job(s) held, work location(s) within the plants, and any other employment or exposure information that is available.

The case-control study may be followed by a more definitive cohort study.

161. CASE-CONTROL STUDY AND OPHTHALMOLOGY SURVEY OF PLANT IN CHARLESTON, W. VA. - NCI

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In response to an employee request, NIOSH began an investigation into an alleged cancer hazard at a DuPont chemical plant in Belle, West Virginia. Subsequent to this employee request, NIOSH received a completed report of a DuPont epidemiologic study that demonstrated an excess risk of cancer of the eye, kidney and lung among employees at the DuPont Belle plant.

In order to thoroughly investigate the causes of this excess cancer risk identified among employees at the DuPont Belle plant, NIOSH proposed to conduct a cross-section ophthalmologic survey of workers at DuPont Belle plant and a case control study of the eye and kidney cancer cases.

The cross-section ophthalmologic survey was conducted from March 13, 1978 to April 21, 1978. A total of 1153 persons were examined. One additional case of ocular melanoma was discovered in a pensioned employee. A follow-up of persons discovered in the course of the survey to have pigmented lesions of the optic fundus is planned for FY 80.

The work histories of all the eye and kidney cancer cases identified at the DuPont Belle plant will be compared to the work histories of a group of matched controls to determine if the cancer cases worked more frequently than the controls in any specific job areas.

162. U.S. CANCER MORTALITY SURVEY

Mason, T. J., Hoover, R. N., Blot, W. J., Stephenson, B. L., Ramsbottom, R. I., Blair, A. E., Fraumeni, J. F., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Environmental Studies Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The objective of this study is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigation to test specific etiologic hypotheses. An analysis of prostatic cancer mortality rates suggested that environmental exposure related to urban living may account for the predisposition of American blacks to this tumor. Respiratory cancer mortality, 1950-69, was consistently high in U.S. counties where shipyards were engaged in the construction and repair of large naval and cargo vessels during World War II. When cell types of leukemia for 1968-71 were analyzed, some clustering of acute myeloid leukemia was seen in the central United States. Ethnic susceptibility appears to account, at least in part, for the regional clustering of kidney cancer and may provide leads to environmental determinants. We are continuing to expand our data sets, both of reported deaths and measures of exposure.

BIBLIOGRAPHIC REFERENCES: Blot, W.J., Fraumeni, J.F., Jr., Morris, L.E.: Patterns of laryngeal cancer in the United States. Lancet 2:674-675, 1978. Blair, A., Fraumeni, J.F., Jr.: Geographic patterns of prostate cancer in the United States. J.N.C.I. 61:1379-1384, 1978.

163. RELATIONSHIP BETWEEN ENDEMIC NEPHRITIS AND KIDNEY CANCER

Milosevic, M. M., Bjelic, P. N., Petrovic, F., University of Belgrade, Inst. of Hygiene & Medical Ecology, *Dr. Subotica St. No. 5, 11000 Belgrade, Yugoslavia*

The aim of the project is to establish the age-adjusted incidence of malignant neoplasms for a seven year period and the relationship between endemic nephritis and cancer of the kidney in an area with 265,000 inhabitants situated in the Serbian Republic on the Morava river.

164. RARE SITES CANCER STUDY

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The objective is the collection, in five metropolitan areas of the United States, of epidemiological data on persons diagnosed as having one of a number of relatively rare cancers. The sites include the vagina, vulva, penis, testis, scrotum, male breast, renal pelvis, adrenal gland, gall bladder, liver, pancreatic islet cell and nasopharynx. All cases diagnosed over the period of study together with an equal number of controls matched by age, sex and race were interviewed in the hospital. The questionnaire included a very detailed investigation of sexual, genital, marital and hormonal factors as well as a large number of environmental agents of possible importance in the pathogenesis of these rare neoplasms. A total of 1,812 rare cancer patients and controls have been identified and interviewed.

165. CLINICAL STUDIES SECTION, BOSTON, MASSACHUSETTS

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The staff of the Clinical Studies Section in Boston, Massachusetts has sifted a large volume of clinical data to identify patients for etiologic studies. These unusual patients are usually found through attendance at clinical conferences and rounds, and through special referrals. With informed consent, epidemiologic studies are made of the environmental and genetic background and laboratory studies are conducted to clarify biologic mechanisms of carcinogenesis. At present, several family aggregates of cancer are under study, e.g., Turcot's syndrome in two

families; Gardner's syndrome variant; breast cancer-Hodgkin's disease aggregation; autosomal dominant renal cell carcinoma associated with a 3:8 chromosome translocation. In addition, a family suffering from mesothelioma following asbestos exposure at a shipyard has prompted two studies of mesothelioma and lung cancers in two New England shipbuilding communities. Also, a computerized Registry of Survivors of Childhood Cancer has been established through collaboration of the Clinical Studies Section with the Sidney Farber Cancer Institute. The 600 registrants represent approximately 2% of all survivors of U.S. childhood cancer in the last two decades. Patients in the series are being studied for second malignancies, cancer in close relatives, and genetic effects in progeny.

166. FIELD STUDIES IN HIGH-RISK AREAS

Blot, W. J., Fraumeni, J. F., Hoover, R., Mason, T. J., Stone, B. J., Pickle, L., Brinton, L., Mendelsohn, L., Morris, L., Lubin, J., Tagnon, I., Day, N. E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Analytical Studies Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The objectives of this project are to identify and describe the environmental determinants of cancer in areas of the U.S. at high risk of cancer through the use of analytic epidemiologic techniques. Toward this end a series of case-control studies has been initiated to test a number of hypotheses regarding the origins of cancer. Presently ongoing are interview studies of lung cancer in northeast Florida; mesothelioma in tidewater Virginia; esophageal cancer in Washington, D.C.; nasal and oral cancer in parts of the South; renal cancer in Minnesota; lung, pancreas, and stomach cancers in southern Louisiana; and lung cancer in eastern Pennsylvania. All areas are at high risk for these tumors. Interviewing was completed during the year for studies of colon cancer in rural Nebraska and lung cancer in coastal Virginia, and data analysis is in progress. A random telephone survey of smoking habits in Georgia showed no coastal excess, highlighting the importance of industrial factors (particularly shipbuilding) in the clustering of lung cancer along the coast, identified by a case-control study of this tumor completed during the year.

BIBLIOGRAPHIC REFERENCES: Blot., W.J. and Fraumeni, J.F., Jr.: Studies of respiratory cancer in high risk communities. J. Occup. Med. 21: 276-278, 1979. Blot, W.J., Stone, B.J., Fraumeni, J.F., Jr., Morris, L.E.: Cancer mortality in U.S. counties with shipyard industries during World War II. Environ. Res. 18: 281-290, 1979.

167. POPULATION BASED STUDY OF LOWER URINARY TRACT TUMORS

Marrett, L. D., Meigs, J. W., Yale University, School of Medicine, Dept. of Epidemiology & Public Health, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

The general purpose of this study is to gain further knowledge about the etiologies of bladder tumor (BT) and other lower urinary tract tumors (LUTT), including tumors of the renal pelvis, ureter, and urethra. The study employs two types of epidemiologic data: 1) interview data on a wide range of possible risk factors; and 2) incidence and mortality data routinely collected by the Connecticut Tumor Registry (CTR).

As part of a large national collaborative study of BT, data about smoking (active and passive), occupational exposures, artificial sweetener and coffee consumption, hair dye use, quality of drinking water, and skin exposures to a variety of medicinal, chemical, and common household products were collected. Four hundred and fifteen (415) cases of BT diagnosed during 1978 and reported to the CTR, as well as a population sample of 880 controls, selected to have the same age and sex distribution as BT cases, have been interviewed.

We are currently extending this study 1) to include cases of LUTT diagnosed between 1/15/78 and 4/15/80 (We expect 100-110 such cases); and 2) to ask all LUTT cases as well as samples of BT cases and controls about their use of analgesics.

The CTR contains demographic and tumor-related data on all malignant neoplasms diagnosed in Connecticut residents since 1935. These will be utilized to examine trends in the incidence and mortality of BT and LUTT.

168. MUTAGENS AND LOWER URINARY TRACT CANCER IN HAWAII

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This case-control study will investigate the association of lower urinary tract cancer with chenical mutagens in the urine in two ethnically distinct groups in Hawaii which have different levels of risk for this disease (high risk for Caucasians and intermediate risk for Japanese). It will also include data on the association of this cancer with smoking cigarettes, drinking coffee, occupational exposures and the use of artificial sweeteners.

Lower urinary tract cancer cases will be identified in the seven major civilian hospitals on Oahu for a period of five years (approximately 104 Caucasian and 92 Japanese cases). We will also recruit surviving prevalent cases who were diagnosed within two years of the start of the study (30 Caucasian and 27 Japanese cases). For each case, two neighborhood controls matched by race, sex and age within five years will be selected and interviewed. Overnight urine samples for a battery of mutagen tests (Ames) will be collected from all subjects.

The questionnaires and format for this study will be similar in design to an ongoing case-control study being conducted by the Harvard School of Public Health in three different populations (including the low risk Japanese in Nagoya, Japan). By this arrangement, we will be able to compare the findings on the Japanese in Hawaii and those in Nagoya in an attempt to identify factors which account for the increase in lower urinary tract cancer among the Japanese in Hawaii. In addition, we will compare data of the Caucasians and Japanese in Hawaii to identify factors which may account for the difference in risk between these two groups which reside on the same island.

169. EPIDEMIOLOGY OF URINARY TRACT CANCER IN GREATER BOMBAY

Jussawalla, D. J., Jain, D. K., Yeole, B. B., Natekar, M. V., Rajagopalan, T. R., Tata Memorial Hospital, Dept. of Surgery & Chemotherapy, *Dr. Ernest Borges Marg, Parel, Bombay 400012, Maharashtra, India*

For this study the data collected by Bombay Cancer Registry for the period 1964-75 have already been reviewed. A total of 954 cases of bladder and kidney cancers have been recorded. The incidence rates for bladder and kidney cancer are 2.8 and 1.3 for males and 0.9 and 0.8 for females, respectively. The incidence and mortality of these cancers by age, sex, religion and histology will be studied and the figures will be compared with those from other registries. A retrospective analysis of these cases will also be carried out in order to study the relationship of urinary tract cancers with smoking habits, alcohol addiction and dietary patterns.

170. POPULATION-BASED STUDY OF LOWER URINARY TRACT TUMORS

Marrett, L. D., Meigs, J. W., Connecticut Cancer Epidemiology Unit, Dept. of Epidemiology & Public Health, *30 College St., New Haven, Connecticut*, 06510, United States of America

The aim is to gain further knowledge of the etiology and epidemiology of bladder tumors (BT) and, more especially, of other lower urinary tract tumors (LUTT) in the State of Connecticut. In particular, the importance of the well documented risk factors for BT in Connecticut and whether passive smoking, common skin exposures, or analgesic abuse are also risk factors, the level of risk, and whether the etiology of LUTT is the same as that of BT will be studied. As part of a national study, data on a large number of suspected risk factors for bladder cancer have been collected by home interview on all new cases of lower urinary tract tumor diagnosed during 1978 in Connecticut residents aged 21-84 at diagnosis and on a random sample of the Connecticut population of the same sex-age distribution as BT cases. Interviews including information on smoking, occupational and industrial exposures, artificial sweetener and coffee consumption, hair dye use, quality of drinking water, passive smoking, and skin exposures to a variety of industrial and household materials have been completed on 415 BT cases, 26 cases of LUTT, and 881 controls. During the next two years additional

cases of LUTT diagnosed in Connecticut will be ascertained using the statewide reporting system which supports the Connecticut Tumor Registry (CTR) to identify cases and the CTR to provide tumor data, giving a total of about 100-110 patients. Cases will be interviewed using the same questionnaire with additional questions on use of analgesics. In addition, a sample of the controls and BT cases and all non-bladder lower urinary tract tumor cases already interviewed will be interviewed again about their use of analgesics.

171. CASE-CONTROL STUDY OF URINARY CANCER, COPENHAGEN

Jensen, O. M., Sorensen, B. L., Clemmesen, J., Knudsen, J. B., Hjalgrim Jensen, S., Finseninstitutet, Danish Cancer Registry, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

Case-control studies of the aetiological role of occupational exposures, and personal habits including smoking, coffee-drinking and use of artifical sweeteners and analgesics by comparing cases of bladder cancer, cancer of the ureter and cancer of the renal pelvis with controls drawn from the general population as well as matched hospital controls for renal pelvis and ureteral cancer are ongoing. Relative risk estimates as well as attributable risks will be derived for each factor individually. The interaction between factors will be investigated.

The final study size will be some 550 cases of bladder cancer, 1100 group matched population controls, and some 150 ureter and pelvis carcinoma-cases to be compared with 450 age- and sex-matched hospital controls. Data collection is estimated to be finished by June 1981.

172. FREQUENCY OF CHAGAS DISEASE IN CANCEROUS PATIENTS

Sacerdote de Lustig, E., Bal, E., Puricelli, L., Lansetti, J. C., Inst. Angel H. Roffo de Oncologia, Dept. of Research, *5481 San Martin Ave., 1417 Buenos Aires, Argentina*

Several authors have demonstrated the oncolytic effect of Trypansoma cruzi, the agent of Chagas disease, on mouse sarcomas and carcinomas. An epidemiological study was designed to study Chagas disease frequency in a group of patients at the Inst. of Oncology Angel H. Roffo in Buenos Aires. Out of 896 patients studied 74 (8.2%) were serologically positive for Chagas, 66.3% of them suffering from malignant tumors and 33.7% with non-cancerous pathologies. Tumor frequency was significantly higher in the Chagasic patients than in the serologically negative ones. When localizations were compared, a higher frequency of esophagus, uterine cervix and urinary system cancers was found in the Chagasic group. The present project is designed to study Chagas disease frequency in a larger group of patients with tumors of the cervix, esophagus and urinary system (bladder and kidney). Sera from patients will be tested by complement fixation, hemoagglutination, latex and immunofluorescence to diagnose Chagas disease. Information on age, anatomopathological diagnosis, place of birth, place of longest residence, cultural and socio-economic level and transfusions will be collected. Approximately 150 patients will be studied.

173. RECURRENT CANCER AND ITS PSYCHOSOCIAL CONSEQUENCES

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The purpose of this study is: 1) to evaluate the psychosocial characteristics of patients with recurrent cancer, 2) to identify those recurrent patients who are at highest risk for emotional distress and poor coping, and 3) to test a screening procedure and two different short-term interventions which previously were proven effective in newly diagnosed patients. Our central hypothesis is that recurrence is more distressing than diagnosis of cancer and that appropriate interventions can significantly reduce levels of distress and fortify coping strategies, especially in case of patients screened as high risk.

Patients from the following cancer site groups will be studied: breast, colon, lung, malignant melanoma, Hodgkin's disease, female reproductive organs (cervix, ovary, uterus), and male genitourinary system (bladder, prostate, testes). These sites offer a wide variety of malignancies, prognoses, treatment modalities, and psychosocial issues. Patients will be assigned to one of three groups, two groups receiving intervention and one a non-intervened control group. Patients will be assessed through interview, rating scales, and psychological testing within the first month of recurrence and then at 2, 4, and 6 months post-recurrence. Interventions will take place following the initial assessment and will continue over a 4-week time period.

III. DIAGNOSIS AND TREATMENT

A. BLADDER CANCER

1. DIAGNOSIS AND PROGNOSIS

174. BIOCHEMICAL AND CYTOLOGICAL ANALYSIS OF EARLY PHASE OF BLADDER CARCINOGENESIS

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OBJECTIVE: Characteristics of human superficial bladder cancer are multicentric tumor occurrence in the bladder and frequent recurrences after transurethrel resection. To solve these problems more information is required concerning the biological features of the urothelium. For this purpose it is useful to study the early phase of bladder carcinogenesis in rats induced by N-butyl-N-(4-hydroxybutyl)nitrosamine, N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide or N-methyl-N-nitrosourea.

APPROACH: We have developed a method to isolate urothelial cells from the rat bladder using EDTA treatment and sonication. We have also found increased agglutinability of urothelial cells by concanavalin A at 1 week after the start of in vivo treatment of rats with various bladder carcinogens. Thus Con A agglutination of bladder cells is a useful method to detect very early phase of bladder carcinogenesis in rats and presently we are studying the effect of promotors for bladder carcinogenesis using this assay system.

175. CYTOLOGIC DETECTION OF BILHARZIAL BLADDER CARCINOMA

El Bolkainy, M. N., National Cancer Inst., *Kasr El-Aini St., Fom El-Khalig, Cairo, Egypt*

A demographic survey has been completed for 10 villages and farms, with a total population of 20,528 individuals. The high-risk group (farmers aged 20 years and above) constituted 25.4% of the entire population. So far, 4 cases of bladder carcinoma have been detected among 1332 persons at risk, a yield of 3/1000, and no tumors have been found among 2736 persons in the low-risk groups. Three tumors were squamous carcinomas and only one was transitional type. Two of the detected tumors were at an early stage (TIS and T1). One case of false positive cytologic diagnosis was made in this series. The overall frequency of bilharzia ova in urine was 12.5%, squamous metaplasia 7.4%, mild dysplasia 6.9%, and moderate to marked dysplasia 0.7%.

176. CYTOLOGIC DETECTION OF CARCINOMA OF THE BILHARZIAL BLADDER

El Bolkainy, M. N., Chu, E., Ghoneim, M. A., National Cancer Inst., Dept. of Pathology, *Kasr El-Aini St., Fom El-Khalig, Cairo, Egypt*

The long-term goal of this project is early detection of carcinoma of the bilharzial urinary bladder. This is attempted by using urinary cytology for selective screening of high risk groups in the population of Egyptian villages, namely farmers aged 20 years and over. An estimated 15,000 persons will be available for study. Of 7,236 persons screened to date seven with confirmed carcinomas were detected. a quality control study to estimate the risk of missing true malignant cases by the screeners has been started. In addition 440 workers in the Elmahalla Textile Company, exposed to aromatic amines for several years and 69.7% of whom had bilharzial infestation, will be screened together with a matched control group of 220 workers not exposed.

177. INVESTIGATION INTO THE USE OF MALIGNANT CELL CYTOLOGY SCREENING FOR BLADDER CANCER IN A CHEMICAL COMPANY

Cartwright, R. A., Gadian, T., Garland, J. B., Yorkshire Regional Cancer Org., *Leeds LS16 6QB, England, United Kingdom*

Routine screening has been undertaken by a chemical company since 1952. The firm had produced carcinogens but

stopped production before that date. The aim of the study is to assess the survival of workmen diagnosed as having bladder cancer after screening as contrasted to those presenting symptomatically. All cases of bladder cancer in workmen have been identified and details of screening recorded as well as their outcome. Cases not industrial in origin but treated contemporaneously have been identified elsewhere in the city and used as a matching group in terms of treatment regimens. The study awaits a few details of follow-up before completion.

178. AUTOMATION OF BLADDER CANCER CYTOLOGY BY TICAS

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Further progress is reported in the system for objective characterization of cells in the human urinary sediment by computer. In additon to 4 previous cell classes for which excellent identifying algorithms have been established, several additional groups of cells were studied with satisfactory discrimination. Initial application of the computer algorithms to visually selected well preserved urothelial cells has been shown to be of diagnostic value in 12 patients. A diagnostic analysis of 13 additional patients is in progress on a small laboratory computer and preliminary results are encouraging. A hierarchiacal analysis of 8 different classes of urothelial cells documented that the cells can be separated into 2 groups, one of which yielded data of diagnostic value. A new method for processing urinary sediment for high resolution scanning has been developed. Further work is in progress in programming small laboratory computer for cell analysis and first attempts at automated full scale analysis of cells in the urinary sediment are planned. The project explores the potential of currently available technology for the cytologic diagnosis of bladder cancer by computer.

BIBLIOGRAPHIC REFERENCES: Koss, L.G.: Urinary cytology - the subjective diagnostic clues and their evaluation by computer. Anal. Quant. Cytol. 1: 202-206, 1979.

179. AUTOMATED URINARY CYTOLOGY FOR CANCER DETECTION

Melamed, M. R., Darzynkiewicz, Z., Sharpless, T. K., Kapuscinski, J., Klein, F. A., Whitmore, W. F., Memorial Hospital for Cancer & Allied Diseases, Dept. of Pathology, *1275 York Ave., New York, New York*, 10021, United States of America

The purpose of this program is to develop flow cytometry instrumentation and cytochemical techniques for automated, quantitative cytologic examinations of exfoliated epithelium of the urinary bladder, lymphocytes from lymph nodes and peripheral blood and tissue culture cells. With our present computer-interfaced flow cytometry instrument system and specially developed fluorescence acridine orange differential staining, we are able to measure DNA, RNA, chromatin structure and nuclear and cellular diameters of cells at rates of several hundred cells per second. In preliminary clinical studies carcinomas of the bladder have been successfully identified from these measurements on exfoliated epithelium in irrigation specimens.

BIBLIOGRAPHIC REFERENCES: Collste, L.G., Darzynkiewicz, Z., Traganos, F., Sharpless, T.K., Sogani, P., Grabstald, H., Whitmore, W.F., Jr. and Melamed, M.R.: Flow cytometry in bladder cancer detection and evaluation using acridine orange metachromatic nucleic acid staining of irrigation cytology specimens. J. Urol, 123:478-485, 1980.

180. INVESTIGATION OF NON-CANCEROUS VESICAL EPITHELIUM BY MEANS OF SELECTED MUCOSAL BIOPSIES IN PATIENTS WITH BLADDER CANCER (ABBREV)

Soloway, M. S., Jordan, W. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This is protocol 2 of the NBCCGA. The protocol was designed to provide data on the incidence of normal and abnormal urothelial changes in grossly endoscopically normal appearing areas of the urinary bladder. No more patients will be placed on this study. Final data is being gathered at this time. A final report will be filed when no more patients treated under this protocol are being followed at the UT-VAH complex.

181. DUPONT CHAMBERS WORKS BLADDER CANCER SCREENING PROGRAM

Vogler, W. J., E.I. du Pont de Nemours & Co. Inc., Research & Development Laboratory, *Deepwater, New Jersey*, 08023, United States of America

OBJECTIVE: Document as thoroughly as possible the operations and results of the DuPont Bladder Cancer Screening Program so as to aid in the evaluation of such screening at the present time. Such documentation of a screening program involves a description of the population which is screened, a description of the screening test and its application to the population, and a description of the results of the interaction between the test and the population in terms of incidence and mortality outcome measures. The product of this investigation will be in two parts. The first is a detailed study of exposure-natural history relationships and estimation of latent period. The second is a characterization of the potential for urinary cytology to detect early bladder cancer and a qualification of the survival experience of cases detected both within and outside the screening program.

182. URINARY CYTOLOGY - FOSSIL FUEL

Jensen, R. H., University of California, Central Office, Lawrence Livermore Lab., *P.O. Box 808, Livermore, California*, 94550, United States of America

The objective of this project is to develop a practical method for automating the cytological examination of exfoliated human bladder epithelium so as to perform rapid and accurate diagnosis of transitional cell carcinoma of the bladder at early stages in the disease. An automated system would be applied routinely to screen urine samples of workers who may be exposed to high levels of carcinogens contained in fossil fuels and products of fossil fuels. To attain this objective we use fluorescent cytochemical probes for cellular DNA, protein, and specific enzymes. The probes label cells in voided urine sediment and allow quantitative analysis by fluorescence microscopy. The increased quantity of DNA in cells with moderate protein content will be used to identify malignant or premalignant urothelial cells in the urine. In addition, the quantity of intracellular proteases will be tested for diagnostic potential. Quantitative fluorescence microscopy also affords the possibility of extracting information about cellular shape, size and texture to aid in providing a complete and accurate diagnosis.

BIBLIOGRAPHIC REFERENCES: Jensen, R.H., et al, Plasminogen Activator as a Diagnostic Marker for Preneoplastic Cells in Human Gynecologic Specimens, Acta. Cytologica 23: 105 (1979). Langlois, R., and Jensen, R., Interactions Between Pairs of DNA-Specific Fluorescent Stains Bound to Mammalian Cells, J. Histochem. Cytochem. 27: 72 (1979).

183. ULTRAFAST SCANNER MICROSCOPE IN LABORATORY AUTOMATION

Shack, R. V., Bartels, P. H., Shoemaker, R. L., Durie, B. G., Buchroeder, R. A., Hillman, D. W., University of Arizona, Graduate School, *Tucson, Arizona*, 85721, United States of America

The objectives of this project are to design, build, and performance test an ultrafast laser scanner microscope capable of acquiring high-resolution image data, at the rate of 60 MHz, for use in automated prescreening for cancer. The fast laser scanner microscope represents a new class of high-resolution microscopes with optics optimized for input into a computer rather than for a human observer. With its data rate of 60 MHz the instrument will be the fastest such device ever designed, and will make it possible to scan a microscope slide area of 2 x 2 cm with 1.6 billion image points within 60 sec. This brings the full information content of high-resolution imagery to bear on the problem of automated cytology at data rates equal to or even greater than those used in flow cytometry, and will make the automated prescreening of cervical and bladder samples feasible once the required special processors are available. The goal for the coming year is to assemble all subsystems of the fast laser scanner and to begin initial performance testing of the system as a whole. This will include tests of the scanner's optical-mechanical performance and of the maintained tolerances. It will include tests of the photometric performance; determinations of effective signal-to-noise ratios and stray light; and operation of the autofocus system under simulated clinical conditions. The

scanned images will be displayed and examined for conformance with scanner design specifications.

BIBLIOGRAPHIC REFERENCES: R. Shack, R. Baker, R. Buchroeder, D. Hillman, R. Shoemaker, and P. H. Bartels, Ultrafast Laser Scanner Microscope, J. Histochem. Cytochem. 27(1):153-159, 1979.

184. SCANNING ELECTRON MICROSCOPY DETECTION OF BLADDER CANCER (HUMAN)

Croft, D. V., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

185. NON-SPECIFIC AND TUMOR-SPECIFIC REACTIVITY IN TUMOR-BEARING HOSTS (HUMANS, RATS)

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We have measured the cytotoxic effects of lymphocytes derived from bladder tumor patients before and after therapy on bladder tumor, normal bladder epithelium and melanoma cell lines, and compared the effects of lymphocytes from healthy donors and tumor patients with types of tumor other than bladder tumor as controls.

The spectrum of reactivity for the different lymphocyte donor groups was the same: the cytotoxic effects were non-specific but selective. The only difference found is that melanoma cells were more sensitive to the effects of lymphocytes of untreated bladder tumor patients than bladder tumor cells of normal bladder epithelium, as compared to the effects of lymphocytes from healthy donors or tumor control patients.

At present we are investigating whether this has to be attributed to a greater susceptibility of melanoma cells for lysis by the lymphocytes of untreated cancer patients with various malignancies. Further experiments are planned to investigate: a) The induction of specific tumor cytotoxicity by co-cultivation of lymphocytes from the different donor groups with tumor cells; b) the relation between the rate of similarity of histocompatibility antigens between the effector cells and target cells and non-specific cytotoxicity of these effector cells; and c) the influence of antigenic modulation of in vitro cultured tumor cells on the cytotoxic effects of different lymphocyte subpopulations.

186. ROLE OF LYMPHOCYTES AND MACROPHAGES IN HOST-TUMOR RELATIONSHIP

Miglietta, A., Liso, V., Antonaci, S., Lucivero, G., Specchia, G., Pansini, N., Universita degli Studi di Bari, Medical School, Inst. of Clinical Medicine, *Policlinico, 70124 Bari, Italy*

OBJECTIVE: Lymphocyte subpopulations, monocytes, and tissue macrophages were studied in order to evaluate their quantitative and/or functional involvement in some groups of tumor patients.

APPROACH: A) Isolation and identification of macrophages from normal and tumor tissues; b) monocyte isolation by adherence; c) identification and purification of lymphocyte subpopulations; d) functional exploration (chemotaxis, natural cytotoxicity) of purified cell populations.

PROGRESS: 1) The number of tumor-infiltrating macrophages was estimated in patients with squamous and basal cell carcinomas. The macrophage content of basal cell tumors was significantly higher than that found in squamous cell carcinomas. The degree of macrophage infiltration was also established in a group of 45 patients with bladder carcinoma. A lower macrophage content seemed to be consistent with a poorer prognosis and a higher frequency of recurrences and/or metastases. 2) Using monocytes and purified lymphocyte subpopulations as effector cells, natural cytotoxicity was found to be higher in non-T and low avidity T-lymphocyte fractions obtained from patients with bladder carcinoma, and such activity could be increased by BCG immunotherapy. 3) T-lymphocytes from a group of patients with B-cell CLL showed decreased response to ConA and PHA, which was restored after addition of autologous monocytes. Moreover, CLL T-lymphocytes failed to help differentiation of normal, PWM-stimulated B-lymphocytes into plasma cells, even when normal monocytes were added to culture. 4) Monocyte and macrophage chemotaxis was performed using as chemotactic agents zymosan-activated fresh serum and a factor obtained by stimulation of cultured leukocytes with ConA. Monocytes from patients with various tumors showed a marked decrease in chemotactic activity, which was almost completely restored after surgical resection of tumor. Macrophages isolated from tumor fragements showed a defective chemotaxis, which was further inhibited by soluble factor(s) obtained from sonicated tumor tissues. Moreover, such factor(s) inhibited chemotaxis of normal macrophages, and monocytes from normal and tumor patients.

187. CHEMICAL AND IMMUNOLOGICAL STUDIES ON CARCINOEMBRYONIC ANTIGEN (CEA)

Hammarstrom, S., Stockholms Universitet, Dept. of Immunology, *Box 6409, S10405 Stockholm 50, Sweden*

OBJECTIVE: To improve the disease related specificity of the CEA-test and to understand the function of CEA and the molecular mechanisms responsible for its appearance in the tumor cell.

APPROACH: Purification and characterization of CEA (colorectal, lung and bladder cancer) and of CEA-related normal adult tissue components. Comparative chemical and immumological analysis of these antigens. Structural studies on CEA. Cleavage of CEA in order to obtain immunologically active fragments. Production of antibodies with restricted CEA-specificity by somatic cell hybridization. Methodological studies on radio- and enzyme immunoassays. Studies on the expression of CEA and related normal antigens on colon carcinoma cell lines.

PROGRESS: A new CEA-related adult tissue component, biliary glycoprotein I (BGPI), was isolated and characterized. BGPI (mol.wt. approximately 85,000) was also detected in serum from healthy individuals (mean value 700 ng/ml). Patients with hepatobiliary diseases have increased BGPI levels in serum. A large N-terminal fragment of CEA (equals CEA low, mol. wt. approximately 125,000) was isolated from liver metastases of colorectal cancer. 'Normal cross-reactive antigen' (NCA) was purified from normal spleen and lung and from tumor. No difference in chemical and immunological properties between NCA from these three sources was seen. NCA appears to be a differentiation antigen in neutrophile granulocytes. It was found at the myelocyte stage. Fragments of CEA with intact disulphide bridges were prepared by trypsin treatment of citraconylated CEA. Several of these fragments were inhibitory in CEA assays utilizing antibodies against protein determinants in CEA. A sensitive and specific radioimmunoassay for CEA was developed. NCA and BGPI at concentrations 10 to the 4th power times higher than those of CEA did not give measurable values. Preliminary evaluation on a small clinical material (approximately 500 sera) showed high cancer specificity of the test.

188. CARCINOEMBRYONIC ANTIGEN STUDIES

Bagshawe, K. D., Charing Cross Hospital, Dept. of Medical Oncology, *Fulham Palace Rd., London, W6 8RF, England, United Kingdom*

OBJECTIVE: To assess the clinical usefulness of carcinoembryonic antigen (1) as a diagnostic aid in patients suspected of having a malignancy and (2) as a means of monitoring patients successfully treated for malignancy.

APPROACH: CEA is being investigated as a diagnostic aid in patients presenting with haematuria and suspected pancreatic disease. The usual diagnostic procedures are carried out and also a plasma specimen, for CEA determination, is taken. CEA is being investigated as an indicator of recurrent carcinoma in patients treated for bladder cancer and colorectal cancer. At each follow-up examination a plasma (and for bladder cancer patients urine) sample is taken for CEA determination. The results are being analyzed.

189. IMMUNODIAGNOSTIC ASSAY OF BLADDER CARCINOMA

Monaco, A. P., Gozzo, J. J., De Fazio, S. R., New England Interstate Water Pollution Control Commission, *607 Boylston St., Boston, Massachusetts,* 02106, United States of America

An assay is needed for the diagnosis of bladder cancer that is sensitive, accurate and suitable for screening high risk populations. Current diagnostic methods involve patient risk and discomfort, are unsuitable for detection of low grade neoplasms or lack specificity. Our previous work suggests that there are tumor-associated antigens (TAA) in the urine of bladder cancer

patients and that detection of these antigens in urine has potential for diagnosis of bladder cancer, even low grade bladder neoplasms. Although one of these antigens is also found in urine of patients with urinary tract infections, other antigens appear to be more specific to bladder cancer.

We propose to continue the biochemical isolation and characterization of these antigens to prepare specific antisera. These antisera will be used to continue the development of an enzyme-linked immunoassay (microELISA), suitable for use in a clinical laboratory. They will also be applied to a study of exfoliated tumor cells in urine by immunofluorescence. Finally, we will quantitate these antigens in the urine of bladder cancer patients and suitable control populations and perform an extended, multi-hospital study to determine the usefulness of our assay in the detection of bladder cancer.

BIBLIOGRAPHIC REFERENCES: O'Brien, P., Gozzo, J.J., Cronin, W. and Monaco, A.P., Qualitative analysis of proteinuria associated with bladder cancer. Invest. Urol. 17:28-32, 1979. O'Brien, P., Gozzo, J.J., Cronin, W.J., and Monaco, A.P. Urinary proteins as biological markers: Bladder cancer diagnosis versus urinary tract infection. J. of Urology (1979), in press.

190. IDENTIFICATION OF ANTIGENS SPECIFIC TO BLADDER CANCER

O'Toole, C. M., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Urology, *62 S. Dunlap St., Memphis, Tennessee*, 38103, United States of America

The project is concerned with identification of the peripheral lymphoid cells with cytolytic activity towards autologous and allogeneic target cells of urothelial origin. Patients with transitional cell carcinoma of bladder (TCC) with localized disease have been shown to have effector cells capable of exerting elevated lysis of the allogeneic cell line T24 (derived from TCC). TCC patients with progressive disease do not exhibit this reactivity. A patient with chronic cystitis with heavy plasma cell infiltrates into the bladder mucosa has been identified who also has effector cells in the blood with selective cytolytic activity toward certain TCC cells in culture. This work is now being extended to search for cytolytic activity toward autologous urothelial cells in patients with TCC and cystitis. The effector cells will be characterized according to conventional surface markers as T, B or null cells.

191. EXPERIMENTAL BLADDER TUMORS

Chapman, W. H., Kiviat, M. D., University of Washington, School of Medicine, Dept. of Urology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The rat model of transitional cell (TC) carcinomas of the urinary bladder has many similarities to the disease in the human. These tumors can be produced by a variety of stimuli (foreign bodies and carcinogens) and have been shown to have common cross-reacting antigens on in vitro measurements of cell mediated cytotoxicity as well as antigens unique to each tumor which can be demonstrated by transplantation immunity experiments.

We would like to investigate the relationship of the common and unique tumor antigens with antigens present in normal transitional epithelium of the bladder, and determine whether the nature of the carcinogenic stimulus makes a difference in the antigens expressed and whether these are neo-antigens. We plan to measure this by both in vivo transplantation experiments and in vitro CMI measurements.

We would like to extend our electron microscopy studies of the mouse bladder to study the EM characteristics (asymmetric unit membrane, desmosomes and A-type virus particles) of these tumors in the rat in vivo and in tissue culture. If an A-type virus similar to that found in the mouse is found to be present in the rat, then evidence for viral antigens would be sought.

192. SPECIFIC ANTIBODIES TO BLADDER CARCINOMA TUMOR ANTIGEN

Pesce, A. J., Evans, A. T., University of Cincinnati, School of Medicine, Dept. of Pathology, *Eden & Bethesda Aves., Cincinnati, Ohio*, 45221, United States of America

The objects of this proposal are to produce antibodies specific for human bladder carcinoma antigens, and to establish whether antibodies are present in these tumors.

The method or approach will be to use bladder cancers, fetal bladder, urine, and urine sediment as possible antigenic sources. Each bladder cancer used will be staged; tumors of Stage III and Stage IV will be used. To increase the yield of tumors and provide a reproducible starting material, additional amounts will be obtained by growing the tumors in athymic (nude) mice. Control antisera will be made from normal tissue. By using immunohistologic and soluble antigen-antibody techniques, and radioisotopically labeled tumor cell membranes, it is hoped that a specific antibody-antigen reaction can be demonstrated which is unique for some bladder tumors. If the specific antibody can be made, it will be tested against tumors of all stages, including Stage I and II.

BIBLIOGRAPHIC REFERENCES: DiPersio, L., Kyriazis, A.P., Michael, J.G., and Pesce, A.J.: Monitoring the Therapy of Human Tumor Xenografts in Nude Mice by the Use of Lactate Dehydrogenase. J. National Cancer Institute 62:375-379, 1979. Kyriazis, A.P., DiPersio, L., Michael, J.G., and Pesce, A.J.: Influence of the Mouse Hepatitis Virus (MHV) Infection on the Growth of Human Tumors in the Athymic Mouse. Int. Journal of Cancer (March 1979), in press.

193. VALUE OF COMPUTERIZED WHOLE-BODY TOMOGRAPHY COMPARED WITH OTHER ROENTGENODIAGNOSTIC METHODS, ULTRASOUND, AND NUCLEAR MEDICINE

Boijsen, E., Lunderquist, A., Tylen, U., Mortensson, W., Ekelund, L., Landberg, T., Lamm, I., University Hospital of Lund, Dept. of Diagnostic Radiology, *E. Blocket, S22185 Lund, Sweden*

The diagnostic results of a third generation CT-scanner with 4.2 seconds of exposure (Philips Tomoscan 300) will be evaluated in relation to other diagnostic modalities. The following subjects are particularly studied:

A) Correlation between ultrasonography, CT, PTC, and angiography in patients with jaundice caused by malignant lesions. The most suitable diagnostic procedure is to be defined.

B) Value of CT in order to define hepatic trauma caused by PTC or PIP (percutaneous transhepatic portography) where CT probably will provide better information than other methods in defining complications.

C) Diagnosis of primary and secondary liver tumors and follow-up after treatment with intraarterial cytostatics, dearterialization and/or liver resection. Diagnosis of primary and secondary liver metastases will be improved with CT combined with infusion of contrast medium into the hepatic artery. Effects of treatment can best be followed with CT combined with intraarterial injection. Different modalities of treatment can be better evaluated with CT.

D) Contrast media and their importance for maximum tumor enhancement in CT. Contrast media are infused in various concentrations and amounts in order to find the proper mode of introduction.

E) Bronchial carcinoma. Evaluation of operability and effects of intraarterial treatment with cytostatics.

F) CT in bladder carcinoma. The main purpose is to improve a clinical evaluation of local spread of bladder tumors.

G) CT in oncology. In order to improve more exact radiation treatment.

194. SCANNING PHOTOMETRY OF HISTOLOGICAL SECTIONS

Grontoft, O., Olofsson, J., University of Linkoping, Dept. of Pathology, *S58183 Linkoping, Sweden*

Previous scanning photometric investigations have disclosed differences in the size and DNA content of the nuclei in normal, dysplastic and carcinomatous laryngeal epithelium. The program used has certain shortcomings when applied to histological sections.

A new program, adapted for examination of sections has been developed, and this pays attention especially to the problems concerning close-lying or touching nuclei and has a variable threshold value which enables a more correct delimitation of the nuclei.

Scanning photometry with this program will be applied to laryngeal dysplasia and carcinoma and to papillary carcinoma of the bladder to assess its value in the diagnosis of different degrees of atypia.

195. ANALYSIS OF URINES FOR NITROSAMINES FROM PATIENTS WITH BILHARZIASIS

Hicks, R. M., Gough, T., Walters, C., University of London, Middlesex Hospital Medical School, School of Pathology, *Riding House St., London W1P 7LD, England, United Kingdom*

There is a high bladder cancer incidence in Egypt, in areas irrigated by canals from the Nile, and it is always linked with endemic bilharziasis. Bilharzial patients also frequently have chronic intractable bacterial infections of the urinary bladder. Many bacteria are capable of reducing nitrate to nitrite, and then nitrosating secondary and tertiary amines to nitrosamines. Secondary amines are normally in human urine. I have suggested, therefore, that nitrosamines could be a factor in the incidence of bladder cancer in Egypt, and if it is so, the bilharziasis is a co-factor, rather than a direct carcinogen. A pilot study has been undertaken with the collaboration of IARC, in which urines from bilharzia infested patients in Cairo and surrounding districts were analyzed by gas chromatography and mass spectrometry. Many of these patients had significantly higher levels of several nitrosamine species in their urines than did uninfested Egyptian and European individuals. For comparison, urines of European patients with chronic bacterial infections of the urinary tract were analyzed in the same way. This investigation will now be extended to other areas where bilharziasis is endemic.

196. DETECTION OF EARLY CARCINOGENESIS IN BLADDER UROTHELIUM (RATS)

Troll, W., New York University, School of Medicine, Dept. of Environmental Medicine, *550 1st Ave., New York, New York,* 10016, United States of America

This is part of a broader project. A summary of this subproject is not available.

197. URINARY GALACTOSYL TRANSFERASE, A POSSIBLE EARLY MARKER ENZYME FOR BLADDER CANCER (ABBREV)

Wolf, G., Massachusetts Inst. of Technology, School of Science, Dept. of Nutrition & Food Science, *77 Massachusetts Ave., Cambridge, Massachusetts,* 02139, United States of America

AIM 1: Study of galactosylretinyl phosphate as an intermediate in tracheal glycoprotein synthesis. (a) Search for an exogenous and endogenous acceptor of galactose in trachea. (b) Investigation of possible lipid-linked oligosaccharide intermediates between galactosylretinyl phosphate and glycoprotein.

AIM 2: Study of galactosyl transferase in bladder cancer in rat and human (with special reference to smoking histories.

198. URINARY PROTEIN COMPONENTS - DIAGNOSTIC AND THEORETICAL

Poulik, M. D., Goodfliesh, R. M., William Beaumont Hospital, *3601 W. 13 Mile Rd., Royal Oaks, Michigan,* 48072, United States of America

Hybridoma antibodies were produced (3 clones) against surface protein(s) of eosinophils and against urinary low molecular weight proteins and post-gamma globulin. The 'eosinophil' antibodies are cytotoxic and their specificity is being established. Bladder tumors were induced in rats by chemical carcinogens and the urines and sera are being tested for levels of rat beta 2-microglobulin (beta 2 m) to test the hypothesis that tumor antigens may have similar overall chemical structure as histocompatibility antigens, namely they also contain beta 2 m as an integral part of their structure. The beta 2 m-blocking test ('bb test') using turkey anti-beta 2m was thoroughly tested and its practical importance became evident. Its use for routine B-cell antigen testing (DR-antigens) enhances the 'specificity' of this type of histocompatibility testing. Cow and horse beta 2-microglobulins were isolated and production of turkey anti-bovine and equine beta 2 m was initiated. These reagents will be very useful in veterinary histocompatibility testing. Urinary post-gamma globulin was studied further and a higher molecular form of this protein was discovered in serum and urine. Isolation, characterization and the mode of its degradation is studied. The presence of this protein in cell membranes in various tissues is being investigated. Search for the biological role of beta 2-microglobulin in embryology is pursued with the aid of antibodies against chicken beta 2 m.

BIBLIOGRAPHIC REFERENCES: Lillehoj, E., and Poulik, M.D.: Beta 2-Microglobulin and Membrane Proteins, Pathology Annual 1979, Vol. 9, pp. 49-80, 1979. Poulik, M.D., Gold, P., and Shuster, J.: Beta 2-Microglobulin: Methods and Clinical Applications, Critical Reviews in Clin. Lab. Sci., Vol. 10, pp. 225-245, 1979.

199. CHROMOSOME ANALYSIS OF HUMAN BLADDER CELL LINES

Hastings, R. J., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A previous report (ICRF Scientific Report 1978 - report 155) described: 1. the ploidy of 5 human bladder carcinoma cell lines; 2. the karyotype of 4 of these lines, EJ, J82, T24 and RT112; and 3. the cloning of the EJ cell line.

The karyotype of the fifth cell line, RT4, shows none of the marker chromosomes seen in the other 4 cell lines. No marker chromosome is common to all 5 cell lines, but there is one normal haploid set of chromosomes present, including the sex chromosomes. Many of the other normal chromosomes are either lost or duplicated but no particular chromosome is consistently involved.

All 3 anaplastic cell lines, EJ, J82 and T24, grow in agar but only EJ and RT112 produced tumors in nude mice. This lack of correlation between the growth in agar and tumorigenicity agrees with those findings of Marshall et al., (Journal of the National Cancer Institute 1977, 58, 1743). However, the three marker chromosomes, M1, M2 and M3, found in the anaplastic cell lines seem to be associated with the expression of growth in agar.

Cloning of the EJ cell line at early passage gave both diploid (beta, 5E and 8D) and tetraploid (2B, 3D, 3E and 9F) clones. The three diploid clones all retained markers, M1, M2 and M3, but varied in the other marker chromosomes present. Clone 8D has a Philadelphia (Ph) chromosome. All 7 clones grow in agar but 2 of these were non-tumorigenic (5E and 3E).

Further analysis with these cell lines and clones may help to explain the relationship between the chromosome constitution of these cells and the expression of a transformed phenotype.

200. CLONAL ANALYSIS OF TUMORIGENICITY IN HUMAN BLADDER TUMOR CELL LINES USING CELL HYBRIDIZATION

Hastings, R. J., Durbin, H., Carbonell, A. W., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The relationship between tumorigenicity, transformed phenotype and chromosome constitution is being investigated using somatic cell hybridization. The first of these experiments has involved two tumorigenic diploid clones, 8D and beta, derived from the human bladder tumor cell-line, EJ. The clones vary in their chromosome constitution; clone 8D has 46 chromosomes and clone beta, 47. The clones differ in their morphology and have different marker chromosomes.

The cells were fused with Polyethyleneglycol 100 and separated on an isometric Ficoll gradient. Ninety-two clones were analyzed chromosomally and the diploid clones discarded. Of the 35 tetraploid clones analyzed, 7 are heterokaryons (8D/beta), 10 are homokaryons (8D/8D) and 1 is a hexaploid heterokaryon (8D/beta/8D). The morphology of these clones varies; 5D is particularly distinctive with large multinucleate cells. The tumorigenicity in nude mice of the 4 hybrids tested so far is as follows: 1D(8D/beta) - 0/3; 4F (8D/8D) - 3/3; 5D (8D/beta/8D) - 1/3; 11E (8D/beta) - 3/3.

Chromosome analysis of the cultured tumors is identical to the original cell inoculum.

Detailed analysis of these clones and tumors and hybridization of near-diploid tumor- and non-tumor-producing EJ clones and normal epithelium and mesenchyme are now in progress.

This project summary contained formulas, drawings, tables or nonkeyable data which are not shown above.

201. INTRANUCLEAR CHROMATIN ORGANIZATION

Rowlatt, C., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Studies of intranuclear chromatin organization in a human bladder tumor cell line (EJ) reported in the ICRF Scientific Report 1978 -report 149, have been continued using transmission electron microscopy at 100kV and 1000kV and viewing stereo

pairs of micrographs. The overall structure seen in critical point dried (CPD) specimens has been confirmed in 0.5 and 1 micrometer sections of Araldite-embedded material, although there is loss of material from the unembedded cells. The Feulgen-type osmium ammine reaction proved a useful DNA stain, allowing changes through mitosis to be followed in 1 micrometer sections at 100kV, but an attempt to exploit the greater resolution at 1000kV in 60nm Araldite sections using this stain to define the DNA molecule (nm diameter) within chromatin proved unsuccessful. Filamentous loops projecting from condensed chromatin seen in the CPD preparations were also found in 60nm sections of embedded material prepared by standard methods. Although present in nuclei in material from several sources, they were most clearly visualized in the isolated nuclear preparations described in Report 154. The improved resolution obtained by using stereo pairs of micrographs at several tilt angles showed that there is a central filament with dense grains in the order of 1nm across, with lateral filamentous projections. These features suggest that the structures are a site of transcription. Enzyme cytochemical studies including phosphatase reactions are also in progress.

202. ANALYSIS OF MALIGNANCY BY MICROCELL-MEDIATED CHROMOSOME TRANSFER

Cowell, J. K., Southgate, J., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Cell lines derived from mouse bladder epithelium show consistent minimal deviations from the normal karyotype (Report 141). These findings are consistent with the view that chromosomal changes may be involved with the expression of the malignant phenotype. Various laboratories have shown that fusion of normal and tumor cells usually results in suppression of the malignant phenotype in the hybrids. Tumorigenic variants from these cells have lost chromosomes. Karyotypic analysis of these variants can be used to assess the role of specific chromosomes in malignancy. Analyses of this kind are complicated by random chromosome loss from the hybrids and the possibility that malignancy may result from the interaction of several chromosomes.

The use in fusion experiments of microcells, which contain one or a few chromosomes, may overcome these problems. Microcells have been prepared from mouse cells using Colchicine and Cytochalasin B treatments (Fournier and Ruddle, Proceedings of the National Academy of Sciences 1977, 74, 319). We are attempting to cross microcells from normal mouse cells with tumor cell lines and vice-versa to assess the importance of individual chromosomes in the expression of the malignant phenotype.

203. AN ANALYSIS OF TRANSFORMATION IN THE BLADDER USING CELL HYBRIDIZATION

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Cell hybridization is a valuable technique for analyzing functional changes in gene expression, particularly the expression of transformed characters. A major disadvantage of hybridization experiments in the past has been the need to use highly selected cell lines with built-in genetic markers that can be used to select against unfused parental cell or homokaryons. A second disadvantage has been the lack of normal epithelial cells for use in experiments concerned with the possible supression of 'malignancy' by normal cells. We have by-passed this second problem by using separated bladder and kidney epithelial cells (see Report 132). Two methods have been used for the selection of hybrids. In one, cells after fusion have been separated into fractions by size on an isokinetic gradient and the large cell fractions cloned. In the second method, each parental clone is treated with a different irreversible biochemical inhibitor (Wright, Experimental Cell Research 1978, 112, 395) so that only heterokaryons will survive. Using these methods we are trying to relate chromosomal changes with tumor production and other transformed characters in mouse and human tumor/tumor and tumor/normal hybrids (see Reports 143-145, 148).

204. CHROMOSOME CHANGES ASSOCIATED WITH TRANSFORMATION OF MOUSE SALIVARY GLAND EPITHELIUM

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Changes in DNA content during in vitro transformation of mouse salivary gland epithelium has been described previously (ICRF Scientific Report 1978 - report 152). All tumorigenic cell lines transformed in vitro, or from tumours induced in vivo, had DNA contents in the subtetraploid range. This has been confirmed using conventional metaphase chromosome preparations and all but one line (from a carcinoma induced in vivo) have modal chromosome numbers in the 63-73 range (2n equals 40). The exception has a bimodal distribution with a sub-octaploid component. A full analysis of the chromosome complement in each cell line, using the trypsin-giemsa banding technique, is nearly complete. It is hoped that consistencies may exist between different lines and that comparisons can be made with information from a similar study of transformed mouse bladder epithelial cell lines (Report 141). It will be of particular interest to follow the development of chromosome patterns typical of these cell lines where stocks are available of the early passage, preneoplastic cells.

205. CHROMOSOMAL AND FLOW CYTOMETRY ANALYSIS IN URINARY BLADDER TRANSITIONAL CARCINOMA

Granberg Ohman, I. F., Collste, L., Wijkstrom, H., Berlin, T., Alim, A., Huddinge Sjukhus, Dept. of Morphology, *S14186 Huddinge, Sweden*

This is a further investigation of the formerly described study on the chromosome constitution and DNA distribution of preinvasive and invasive papillary bladder carcinoma. There is a good correlation between ploidy, the presence of markers and the histopathological grade of differentiation. So far no specific chromosome aberration typical of this tumor has been found. In recidivistic tumors also, no histological progress has been observed so far in the tumors investigated. In all new tumors the chromosome pictures were like the one observed in the primary lesion.

One papillary tumor grade was studied separately and these particular results will be published. The mode was in the pentaploid region and almost all metaphases had 1 to more than 100 double-minutes (dms), negative in C-banding analysis. Even though this study was of a papillary tumor grade 3, the findings differ significantly from the findings in all bladder tumors investigated.

206. PLOIDY AND PROLIFERATION IN HUMAN BLADDER CARCINOMA AS MEASURED BY FLOW-CYTOFLUOROMETRIC DNA-ANALYSIS (ABBREV)

Tribukait, B., Edsmyr, F., Gustafson, H., Andersson, L. O., Esposti, P., Karolinska Institutet, Dept. of Medical Radiobiology, *Solnavagen 1, S10401 Stockholm 60, Sweden*

Quantitative flow microfluorometric DNA analysis provides possibilities for determining degree of ploidy and proliferation rate in tumor specimen and exfoliated tumor cells. The technique has been used in studying bladder neoplasms. A relationship between degree of ploidy and proliferation, and the histological picture and the clinical stage of bladder tumors has been found. The significance of these results for the development of the disease is analyzed in a follow-up study of 400 patients.

207. CHROMOSOMES OF HUMAN BLADDER TUMORS

Sandberg, A. A., Beckley, S., Matsui, S., Roswell Park Memorial Inst., Dept. of Genetics/Endocrinology, *666 Elm St., Buffalo, New York*, 14263, United States of America

During the last year and in the forthcoming years not only will previously undertaken studies be continued on the chromosome findings in bladder cancer, but other areas into which the study has been extended will be investigated including the determination of centromeric heterochromatin polymorphism in the tumor and somatic (lymphocytes) cells of patients with bladder cancer, the study of the ultrastructure of such heterochromatin in an attempt to possibly establish some specificity in the case of bladder cancers, and undertaking of a comprehensive cytogenetic evaluation of non-invasive and sub-mucosally inva-

sive tumors supplied to our laboratory from about half-a-dozen centers involved in the study of patients with bladder cancer, with major emphasis being placed on follow-up of such patients, both clinically and cytogenetically.

This study continues to be concerned with establishing detailed karyotypic aspects of cancer of the bladder with particular emphasis on papillary tumors. Cytogenetic criteria of help to the clinician in predicting possible recurrence of papillary tumors, such as the presence of marker chromosomes and other structural anomalies, have received and will continue to receive primary attention. A study based on the staining of rDNA of the acrocentric chromosomes and the application of this technique to the establishment of subtle translocations involving such chromosomes is now being utilized in our laboratory.

Another aspect of the study is correlation of transitional cell cancers of the bladder and a correlation of the cytogenetic findings with therapeutic and biologic behavior of these cancers. Emphasis is being put on the changes involving certain chromosome groups, e.g., No. 1 and No. 14, as biologic indicators of the behavior of such tumors.

BIBLIOGRAPHIC REFERENCES: Sandberg, Avery A.: The Chromosomes in Human Cancer and Leukemia. Elsevier North-Holland, Inc., New York, 1980. Sandberg, A.A.: Some comments on sister chromatid exchange (SCE) in human neoplasia. Cancer Genet. Cytogenet. in press, 1980.

208. ANALYSIS OF THE IMMUNE RESPONSE TO MALIGNANT TUMORS OF THE URINARY BLADDER

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OBJECTIVE: Analysis of tumor-directed immune responses in patients with transitional cell carcinoma of the urinary bladder (TCC), aiming at 1) elucidating their possible significance for the clinical course of the disease, and 2) developing immunological tests for monitoring patients.

APPROACH: Cellular and humoral in vitro tests with bladder tumor cells in tissue culture and with serum and lymphocytes from patients. Immunochemical analysis of plasma membranes of bladder tumor cells, isolation, purification and characterization of tumor-associated antigens.

PROGRESS: Blood lymphocytes from patients with TCC are cytotoxic to bladder tumor cells in vitro. A disease-related cytotoxicity is primarily seen in patients not previously treated for their disease. On the average, approximately 60 percent of the reactions against allogeneic tumor cells reflect an antibody-dependent cell-mediated cytotoxicity, induced by both natural and disease-related antibodies of the patients. In parallel, there occurs an antibody-independent cytotoxicity of undefined specificity as well as a specific and HLA-restricted T-cell-mediated cytotoxicity. Attempts are now made to further delineate the specificities of these reactions and to elucidate which of the different immunological effector mechanisms predominate during different phases of disease.

209. EVALUATION OF CHEMOTHERAPY RESPONSE OF INDIVIDUAL PATIENTS' TUMORS

Herman, C. H., Vooys, G. P., University Hospital of Nijmegen, Dept. of Pathology, *Geert Grooteplein 10, 6525 GA Nijmegen, Netherlands*

OBJECTIVE: Development of reliable, reproducible automated tumor stem cell assay for routine evaluation of patients' tumor responses to chemotherapy.

APPROACH: Breast and bladder tumors are explanted by the tumor stem cell assay method developed by S.E. Salmon and associates, with and without chemotherapeutic agents currently used in EDRTC protocols for bladder tumors and by the Nijmegen Cancer Center for breast tumors. Analysis of the cultures for decreased colony/cluster formation is by an automated image processing system (Omnicon FAS II, Bausch and Lomb, Rochester, NY, USA) dedicated to this application. In this initial stage, comparison between in vivo and in vitro tumor responses is assessed.

210. STUDIES OF THERAPEUTIC END RESULTS AND PROGNOSTIC FACTORS

Myers, M. H., Stanek, E. J., Hankey, B. F., Prorok, P. C., Chen, J. S., Heise, H. W., Connelly, R. R., Baranovsky, A., Silverman, D. T., Devesa, S. S., Steinhorn, S. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Biometric Research & Analytic Studies Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Ten-year follow-up results from the HIP study of screening for breast cancer have shown that the screened group experienced 1/3 less mortality from breast cancer than the control group. This reduction appeared to be concentrated in women over 50. The associations of cancer incidence with income and education were studied. Among whites, strong negative associations were observed for esophageal, stomach, lung and cervical cancer, with positive associations for colon, bladder and breast cancer. An analysis of TNCS and SEER data showed that for white males the incidence rate of mesothelioma has increased in recent years. The development of methodology for the evaluation of screening programs has demonstrated new age dependent characteristics of lead time and length bias. Appropriate variables to use in the analysis of randomized screening trials were defined. A study of suicides among cancer patients indicated that male patients were at twice their expected risk of suicide while females were not at excess risk. The relationship of the levels of selected urinary steroid metabolites to breast cancer recurrence subsequent to radical mastectomy was studied: relationships were observed only for postmenopausal patients.

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211. DETECTION OF CIRCULATING ANTIBODIES AND ANTIGEN-ANTIBODY COMPLEXES

Burger, D., Washington State University, School of Veterinary Medicine, Dept. of Veterinary Microbiology & Pathology, *Pullman, Washington*, 99163, United States of America

OBJECTIVE: Purify antigen-antibody complexes by affinity chromatography.

APPROACH: Using feline leukemia or induced bladder tumors in rats, immune complexes will be isolated from the serum of affected animals. Possible correlation between quantities of complexed antibody in serum and progression of tumor will be evaluated. Complexes will be evaluated for blocking activity.

2. CHEMOTHERAPY

212. TOPICAL MITOMYCIN C THERAPY OF URINARY BLADDER TUMORS

Soloway, M. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

Clinical trials evaluating Mitomycin C (MMC) over the past year have proven very favorable. The main objectives of this study were to determine efficacy of a new intravesical chemotherapy for superficial bladder tumors and whether absorption of the drug occurs. Thirteen patients have received a full course of MMC and there have been eight complete responses. These patients have been continued on monthly Mitomycin C with no further recurrence. It has also been found that Mitomycin C is not absorbed. This protocol will be continued.

213. PHASE II STUDY OF HEXAMETHYLMELAMINE IN REFRACTORY BLADDER CANCER

Einhorn, L. H., Williams, S. D., Stevens, E., Bond, W. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1481 W. 10th St., Indianapolis, Indiana*, 46202, United States of America

Patients with metastatic bladder cancer of all cell types will be treated with HMM. Appropriate laboratory studies will be performed. All patients will be required to have measurable disease. The end points of the study are objective tumor response in survival and toxicity.

214. SWOG-7904, HEXAMETHYLMELAMINE VS. FAC IN ADVANCED BLADDER CARCINOMA IN PATIENTS WITH IMPAIRED RENAL FUNCTION, PHASE II, III (ABBREV)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This study is designed to compare the effectiveness of Hexamethylmelamine vs. FAC (5-Fluorouracil, adriamycin, and cyclophosphamide) in the treatment of locally recurrent or disseminated transitional cell carcinoma of the bladder. Both good and poor arrest patients will be randomly assigned to one or the other arm of the treatment and at the time of treatment failure, they will be crossed over to the other drug or combination. The FAC combination is made up of drugs, all of which are active in bladder cancer. There is some data suggesting that Hexamethylmelamine may have activity in bladder cancer and with this in mind, it will be tested up front in a randomized crossover study with FAC.

215. ADRIBLASTINA (ADRIAMYCIN) IN THE PREVENTION OF RECURRENCE OF SUPERFICIAL BLADDER TUMORS

Souto, C. V., Mariano, M., ENF, Urologia 31, *Sta. Casa de Misericordia, Porto Alegre 90000, Brazil*

OBJECTIVE: To determine whether adriamycin reduces the percentage of recurrence of tumors of the vesical epithelium.

APPROACH: Patients with superficial bladder tumors are randomized to two groups: A. The control group which receives no treatment other than periodic cystoscopy. B. The treated group which receives intravesical adriamycin and also undergoes cystoscopy.

216. A RANDOMIZED COMPARISON OF THIO-TEPA AND MITOMYCIN AS TOPICAL THERAPY IN NON-INVASIVE BLADDER CANCER

Soloway, M. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

Until recently, thio-TEPA was the primary drug utilized for intravesical chemotherapy in patients with superficial bladder cancer. Clinical trials using mitomycin C were conducted and documented the activity of this drug in superficial bladder cancer. A prospective trial randomizing patients with histologically documented transitional cell carcinoma between thio-TEPA and mitomycin C has been initiated to compare the relative efficacy of these two agents. Response rates as well as toxicity will be evaluated and compared.

217. EVALUATION OF CISDIAMMINEDICHLOROPLATINUM II IN PATIENTS WITH ADVANCED CARCINOMA OF THE URINARY BLADDER

Soloway, M. S., Clair, C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This protocol is designed to compare the response rate of advanced carcinoma of the urinary bladder to either Cisdiamminedichloroplatinum II (DDP) or DDP plus Cytoxan. Animal studies using a murine bladder cancer have shown an antitumor effect by the combination. Clinical studies to date have not clarified the situation. In addition to the response rates and survival from the two regimens, the toxicity resulting from adding Cytoxan to DDP will be carefully monitored. The major purpose of this study is to evaluate the response of the tumor to these regimens as a preliminary to possible use of the adjuvant setting. In this study, patients eligible for the protocol will either have measurable metastatic bladder cancer or locally extensive bladder cancer not amenable to definitive radiotherapy or radical surgery. There is an initial 9 week evaluation period with stable patients being continued on the regimen and patients progressing being taken off the protocol. To date 39 patients have been entered from the VA and UT, and 161 from all participating institutions. This is an active protocol, and patients continue to be randomized.

218. ADJUVANT CHEMOTHERAPY IN BLADDER CARCINOMA

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study is designed to investigate the value of adjuvant therapy in patients with Group II carcinoma of the bladder (bladder wall infiltrated with local lymph node involvement at the time of surgery). Patients were to be randomized to no treatment or a combination of Cytoxan and 5-FU. The study is closed as the number of patients entered was too small for significant results.

219. A PHASE II TRIAL OF MITOMYCIN C AS TOPICAL THERAPY IN NON-INVASIVE BLADDER CANCER AFTER FAILURE ON THIO-TEPA

Soloway, M. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

The use of Mitomycin C after thio-TEPA failure has proven to be of definite value to patients placed on this study. Of the patients placed on this protocol all but one patient have shown at least a partial, if not complete, response with minimal side effects to the drug. In utilizing Mitomycin C as a topical therapy in noninvasive bladder cancer, the effect rate has reduced surgical intervention, thus decreasing hospitalization and anesthesia, which is not well tolerated by elderly patients and/or patients with other medical illnesses.

220. PHASE III RANDOMIZED STUDY OF COMBINATION CHEMOTHERAPY VS. SINGLE AGENT CIS-PLATINUM IN METASTATIC BLADDER CANCER (ABBREV)

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This is a randomization of Cytoxan, adriamycin and cis-platinum vs. cis-platinum alone in metastatic bladder cancer. This protocol will entail a randomization between Cytoxan, adriamycin and cis-platinum in combination every three weeks, vs. cis-platinum alone. Responders to therapy will be continued on the chemotherapeutic regimen for an additional 8 courses as a maintenance therapy. It is hoped that, as a result of this protocol, we will be able to answer the question whether combination chemotherapy is better than one of the better single agents - cis-platinum alone - in the treatment of metastatic bladder cancer.

221. ADJUVANT CHEMOTHERAPY OF TRANSITIONAL CARCINOMA OF THE BLADDER

Einhorn, L. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1481 W. 10th St., Indianapolis, Indiana*, 46202, United States of America

PROJECT OBJECTIVES: To determine the efficacy of adjuvant chemotherapy with Platinum, Adriamycin and Cytoxan in patients with transitional carcinoma of the bladder initially treated with 'standard' irradiation and surgery.

PLAN: All patients with biopsy proven transitional carcinoma of the bladder will be clinically staged and then if appropriate, they will receive pre-operative radiation therapy followed by laparotomy, cystectomy and pelvic node dissection. Then the patients will be randomized to receive or not to receive chemotherapy with Platinum, Adriamycin and Cytoxan.

METHODOLOGY: Patients meeting the above criteria will be eligible for this study. The groups will be compared for disease-free interval and overall survival.

RESULTS TO DATE: Two patients treated with one complete remission and one non-responder.

222. SOUTHWEST ONCOLOGY GROUP PROTOCOLS 7624, 7619, 7522, 7410

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

7624: This study of adriamycin vs. adriamycin plus cis-platinum in bladder cancer has six case entries. A Southwest Group-wide study has a total of 105 case entries and at the present time there is no significant difference with respect to survival or disease-free survival between the two regimens.

7619: No institutional patients have been entered in this study.

7522: One VA patient has been added to this study which compares chemotherapy with or without BCG plus optional splenectomy in chronic myelogenous leukemia. This study is currently undergoing final analysis and is closed to further entry.

7410: There are two patients entered into this groupwide study using cytoxin, adriamycin, and prednisone for chronic lymphocytic leukemia. Study is now closed for further case entry and the final analysis is underway.

223. COMBINATION CHEMOTHERAPY OF ADVANCED BLADDER CARCINOMA

Coates, A. S., Freedman, A., Himpoo, B., Sarfaty, G. A., Prince of Wales Hospital, Special Unit for Investigation & Treatment, *Avoca St., Randwick, N.S.W., Australia*

OBJECTIVE: Phase II study of effectiveness of a combination of cis-platinum diammine dichloride (CPDD), adriamycin (ADR) and cyclophosphamide (CTX) in the treatment of recurrent or metastatic bladder cancer, as shown by response rate, response duration and survival.

APPROACH: Eligible patients will have histologically confirmed bladder carcinoma with measurable recurrence of metastasis not suitable for resection or local radiotherapy. This is a non-randomized phase II study. Dosages are CPDD 70 mg/m2 IV (with hydration and mannitol diuresis); ADR 30mg/m2 IV; CTX 250 mg/m2 IV. Cycle repeated each 3-4 weeks.

PROGRESS: New study.

224. CYCLOPHOSPHAMIDE, ADRIAMYCIN AND PLATINUM IN BLADDER CARCINOMA (HUMAN)

Hemstreet, G. P., University of Alabama in Birmingham, School of Medicine, Dept. of Surgery, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

This is part of a broader project. A summary of this subproject is not available.

225. CHEMOTHERAPY OF METASTATIC BLADDER AND KIDNEY CANCER

Hahn, R. G., DeWeerd, J. H., Edmonson, J. H., Kvols, L. K., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

Despite some progress in defining several agents with antitumor activity against bladder cancer, continued search for new single and combination agent activity in this tumor system is indicated. The proposed protocol employing VP-16 or cis-platinum will attempt to identify the antitumor activity of these agents in a prospective randomized Phase II trial in patients with clearly measurable metastatic or advanced bladder cancer. This protocol trial will be conducted as a member of the group representing the Confederation of the National Bladder Cancer Project. The common arm for the confederation study will be that of cis-platinum with VP-16 representing the alternative agent under study by the Mayo Clinic.

226. BLADDER CANCER CHEMOTHERAPY - TRYPTOPHAN METABOLISM

Carlton, C. E., Newman, A. J., Baylor College of Medicine, School of Medicine, Dept. of Surgery, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

The objective of this research proposal is to study the recurrence rate of bladder tumors in patients following correction of abnormal tryptophan metabolism. This investigation will concentrate on those tumor patients showing an abnormal urinary excretion pattern of tryptophan metabolites following an oral tryptophan load. Clinical trials will evaluate the effect of pyridoxine (vitamin B6) on recurrence rate of bladder tumors.

The methods employed will be: 1) selection of patients with Grade O or A tumors; 2) analysis of 24-hour urinary tryptophan metabolites before and after the ingestion of L-tryptophan; and 3) clinical trials utilizing pyridoxine and placebo in a double-blind study.

The purpose of the research is to elucidate the long-term recurrence rate of heterotopic bladder tumors in those patients whose abnormal tryptophan metabolism has been corrected.

227. INTRAVESICAL CHEMOTHERAPY OF BLADDER CANCER

Soloway, M. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee,* 38104, United States of America

Intravesical chemotherapy is being increasingly utilized both for definitive therapy of superficial bladder tumors and as prophylaxis following endoscopic resection or fulguration of all visible neoplasms with the hope of reducing the high rate of subsequent tumor formation. Without using prophylactic intravesical chemotherapy the 'recurrence' rate is approximately 60 percent. Trauma to the urothelium may be a factor in allowing tumor cells to implant and be a major factor in this high rate of subsequent tumors. We have established a technique to reproducibly cauterize portion of the murine bladder and following instillation of transitional tumor cells implantation will frequently occur. Implantation does not occur if the same number of tumor cells are placed in contact with the normal murine urothelium. Using this as a model, the effects of thio-TEPA, mitomycin C, and cis-platinum have been compared in regard to their efficacy of preventing tumor implantation. The control group had a tumor incidence of 78 percent. Both thio-TEPA and mitomycin reduced the incidence of tumors, 36 percent and 33 percent, respectively; p less than 0.02. DDP intravesical therapy completely prevented tumor implantation.

A series of studies evaluated the effect of intravesical chemotherapy on primary FANFT-induced bladder tumors. The same intravesical chemotherapeutic agents as mentioned above were given weekly for 4 weeks. The controls (FANFT only) had a tumor incidence of 96 percent. DDP reduced the incidence of tumors to 40 percent. Mice receiving thio-TEPA and mitomycin had an incidence of 71 percent. Current studies are evaluating the effect of adriamycin and/or mitomycin C on the ability to prevent FANFT-induced tumors.

It is hoped that this approach can continue to provide data that correlate with those obtained in man. To date, drugs effective in the animal have shown similar activity in man.

228. CHEMOTHERAPY OF HUMAN BLADDER CANCER IN ATHYMIC MICE

Kyriazis, A. P., Pesce, A. J., University of Cincinnati, School of Medicine, Dept. of Pathology, *Eden & Bethesda Aves., Cincinnati, Ohio,* 45221, United States of America

The purpose of the present study is to investigate the effect of single agent and combination chemotherapy on human bladder transitional cell carcinomas by using the nude mouse/human tumor xenograft system. To achieve this goal established tumor lines will be transplanted into nude mice. Initiation of treatment will begin when tumors reach a size of 1 cm3. Treatment evaluation will be based primarily on tumor growth curves and histopathological changes. Various combination treatments and the significance the sequence of the chemotherapeutic compounds may have on tumor response will also be studied. An effort will be made to evaluate tumor response in relation to tumor grade and stage of the disease.

229. EXPERIMENTAL CHEMOTHERAPY OF MURINE BLADDER CANCER

Soloway, M. S., Murphy, W. M., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Urology, *62 S. Dunlap St., Memphis, Tennessee,* 38103, United States of America

The prognosis for patients with advanced carcinoma of the urinary bladder remains poor despite surgery and/or radiation therapy. Chemotherapy has not been incorporated into the armamentarium of the urologist or oncologist treating these patients because of limited clinical data. Few drugs have been definitively evaluated in patients with bladder cancer. In an attempt to provide this information an animal model employing the bladder carcinogen N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide (FANFT) in syngeneic mice is being used to screen agents for activity. FANFT-induced tumors resemble their human counterparts both grossly and histologically.

Transitional cell tumor transplants representing the spectrum of bladder tumors (poorly differentiated, high grade to well differentiated, low grade) will continue to be established. The responsiveness of these transplants to single and combination chemotherapy will be evaluated and correlated with their

growth patterns and histologic appearance. The optimal irradiation dose has been determined for one of these tumors. Possible potentiation of radiotherapy by concomitant chemotherapy will be evaluated.

Since treatment of primary FANFT-induced tumors most closely simulates the situation in man, single and selected combination chemotherapy and/or radiotherapy will be given to mice ingesting FANFT and their effectiveness in reducing the incidence, size, stage, and grade of bladder cancer determined.

Intravesical chemotherapy (I.V.) will be evaluated by determining 1) which drugs are capable of inhibiting tumor cells from implanting on the inflammed murine urothelium, and 2) whether long-term I.V. will alter the incidence or stage of primary FANFT-induced tumor.

230. MULTISTAGE CARCINOGENESIS IN THE RAT URINARY BLADDER - FURTHER INVESTIGATION OF THE PROMOTION PHASE

Hicks, R. M., University of London, Middlesex Hospital Medical School, School of Pathology, Dept. of Cell Pathology, *Riding House St., London W1P 7LD, England, United Kingdom*

OBJECTIVE: To investigate the ability of alkylating agents and therapeutic drugs such as methylmethane sulphonate, cyclophosphamide, thiotepa and epodyl to promote tumor growth in an initiated urothelium.

APPROACH: Rats are given an initiating (sub-carcinogenic) dose of the carcinogen methylnitrosourea by a single intravesicular instillation into the urinary bladder. They are then subjected to prolonged treatment with the alkylating agent under investigation for promoting activity. Appropriate controls are established which receive either the initiating carcinogen alone or the suspect promoting agent alone. Tumor incidence is recorded after maintaining the animals for 2 years. The histology and ultrastructure of the urothelium are studied and the results are compared to assess pathological change attributable to each drug per se, and in combination with the initiator.

PROGRESS: Some experiments are completed but the histopathology has still to be assessed. Work with methylmethane sulphonate has already been started and the animals will be maintained for another 20 months before killing.

231. IN VITRO SENSITIVITY OF ESTABLISHED CELL LINES DERIVED FROM HUMAN BLADDER TUMORS TO CHEMOTHERAPEUTIC DRUGS

Hepburn, P. J., Masters, J. R., University of London, Dept. of Pathology, Inst. of Urology, *St. Paul's Hospital, 24 Endell Street, London WC2, England, United Kingdom*

OBJECTIVE: To determine whether established cell lines derived from human bladder tumors provide a model system for bladder cancer therapy.

APPROACH: The chemosensitivities of ten well-characterized established cell lines to chemotherapeutic drugs used to treat advanced bladder cancer are being compared using clonogenic assays.

PROGRESS: The colony forming efficiencies of the cell lines on plastic and 3T3 monolayers, and the growth patterns (determined using 3HTdR uptake) have been determined. Comparisons of various forms of clonogenic assay indicate that the most suitable system for all the cell lines is transfer to 3T3 feeder layers following drug treatment.

232. IN VITRO CHEMOTHERAPY TESTING IN BLADDER CARCINOMA

Weaver, D. J., Adelstein, E., Ross, G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *800 Stadium Rd., Columbia, Missouri*, 65201, United States of America

PROJECT OBJECTIVES: (1) To grow primary human bladder tumors and test them in vitro with single chemotherapeutic agents to determine drug sensitivity; (2) to use established human and animal bladder cancer lines to develop new assays for drug sensitivity testing; (3) to develop sequential and combination chemotherapeutic regimens based on previous morphological ultrastructural studies and to evaluate these drug combinations by morphological and in vitro cell damage assays.

PLAN: Bladder tumors (primary human and animal and human lines) are separated into single cells and drug sensitivity measured by chromium-51 release and tritiated thymidine uptake. These studies are carried out in a microtiter format. Sequential and combination drug studies are evaluated by the above in vitro methods, as well as by ultrastructural studies carried out by directly fixing and examining the cells on the plastic surface.

METHOD: These studies use an automated cell harvester to measure chromium release and tritiated thymidine uptake. Transmission electron microscopy and inverted phase microscopy are used to study morphological changes.

CLINICAL RELATIONSHIP: This area of research is highly relevant to the treatment of bladder cancer by the instillation of specific drug combinations that in in vitro testing would indicate specific anti-tumor activity.

233. CLONAL ASSAY AND CHEMOTHERAPY OF UROTHELIAL CANCER

Stanisic, T. H., Salmon, S. E., Meyskens, F. L., Alberts, D. S., Davis, J., Rowland, R., Drach, G. W., Sethney, H. T., Lewis, D. B., Benson, B., Nagle, R., Moon, T., University of Arizona, School of Medicine, Dept. of Surgery, *1501 N. Campbell Ave., Tucson, Arizona*, 85721, United States of America

An in vitro clonal assay already shown to be useful in the study of other neoplasms will be directly applied to the study of bladder cancer. Urothelial cells, obtained by tumor biopsy and bladder barbotage, from bladder cancer patients will be exposed to cytotoxic agents in vitro. Subsequent reduction in the clonogenic capacity of these cells will be used as a measure of drug sensitivity of each patient's bladder cancer cells. In vitro drug sensitivity will be correlated with in vivo drug sensitivity for each patient specifically. We will ultimately use such information to develop an individualized predictive approach to the chemotherapy of transitional cell carcinoma.

In addition, the differential ability of neoplastic and normal urothelial cells to form clonal aggregates will be examined in detail. Clonal aggregates from 'normal' and bladder cancer patient will be examined by means of light and electron microscopy, chromosomal studies and ABO antigenic studies with the aim of developing a specific and sensitive indicator of the biologic potential of the urothelium.

3. IMMUNOTHERAPY

234. INTERFERON - EFFECT ON IMMUNITY TO BLADDER TUMORS

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The objective of our proposed research is to define the effect of Type II interferon on the cell-mediated immune response to bladder tumors and compare it with the effect of Type I interferon. To this end we will test the effect of interferon (both Type I and Type II) treatment in vitro on human mononuclear cells isolated from the peripheral blood for: (1) Effect on antibody-dependent cell-mediated cytotoxicity using 253J human bladder cancer cells, (2) effect on natural killer cell activity using K562 human lymphoma and 253J target cells, (3) effect on the generation specific T cell mediated cytotoxicity against 253J target cells. In addition, a murine animal model system will be developed using the FANFT-induced bladder tumor, MBT-2, to evaluate the effect of interferon (Type I and Type II) in vivo and in vitro on the cell-mediated cytotoxic mechanisms listed above using appropriate mouse target cells including MBT-2 cells. Moreover, the effect of interferon-induced modulation of the immune response on the growth of transplanted MBT-2 bladder tumors in syngeneic mice will be evaluated.

We will determine the dose and class (Type I or Type II) of interferon most effective for modulation of the cell-mediated responses in vitro for both the human and murine models and in vivo for the murine model. Moreover, we will determine the most effective dose and class of interferon (Type I or Type II) for prevention of the growth of transplanted MBT-2 tumors in syngeneic mice.

We will determine the effect of interferon (Type I and Type II) on the induction of primary murine bladder tumors by FANFT.

235. BCG IMMUNOTHERAPY OF RECURRENT SUPERFICIAL BLADDER CANCER

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Since January of 1978, 57 patients with transitional cell carcinoma of the bladder have enrolled in a randomized, prospective evaluation of intravesical and percutaneous BCG immunotherapy. Immunotherapy consisted of six 120 mg intravesical and 5 mg percutaneous Pasteur strain BCG administrations at weekly intervals as described by Morales et al. Side effects of BCG therapy are minimal, with approximately 91% mild dysuria, 83% urinary frequency, 39% mild gross hematuria, 22% low grade fever, and 17% nausea or vomiting. No disseminated BCG infection, allergic reaction, hepatic toxicity or cytopenia was observed and no patient required postponement of BCG treatments. Comparing the overall recurrence rate between groups, in the control group 46% had recurrent tumor, compared with 22% of the treated patients. Tumor recurrence was delayed with BCG therapy. Mean time to recurrence in the control is 12 months compared with 19.4 months after BCG (p equals 0.016, Wilcoxon). Immunological evaluation suggests that those who fail to develop cellular or humoral immunity to BCG related antigens have tumor recurrence at the same rate as controls: only 7% who converted PPD skin test and tumor recurrence compared with 44% of those who did not (p equals 0.056). Four of 5 BCG treatment failures had no in vitro immunity to PPD at the time of recurrence, and 2 of 5 had impaired humoral antibody response.

236. BCG IMMUNOTHERAPY - RECURRENT SUPERFICIAL BLADDER CANCER

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OBJECTIVE: Evaluate in a controlled, randomized prospective study the therapeutic efficacy of intravesical and percutaneous BCG in patients with recurrent superficial bladder cancer. The administration of BCG shall be identical to the methods published in the J. of Urology 116: 180-183, 1976. It is expected that 32 patients per year will enter the study. Any modification of the protocol design must have the prior approval of the Project Officer before being instituted.

237. BCG IMMUNOTHERAPY OF SUPERFICIAL BLADDER CANCER

Lamm, D. L., Thor, D. E., Smith, K. O., Harris, S. C., Radwin, H. M., Novicki, D. E., Winters, W. D., McMahan, C. A., University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Surgery, *7703 Floyd Curl Dr., San Antonio, Texas*, 78284, United States of America

In an ongoing NCI contracted study, the authors have demonstrated that simultaneously administered intravesical and percutaneous BCG immunotherapy significantly (p equals 0.029, chi square) decreases the rate of recurrence of transitional cell carcinoma compared with controls. The duration of protection afforded by BCG immunotherapy, and the optimum dose, route, and frequency of BCG administration remain to be determined and are the primary objectives of this proposal. In addition, utilizing a murine bladder cancer model we have demonstrated that excessive BCG administration can impair the antitumor response or even enhance tumor growth, as has been seen by other investigators with different tumor models. It is critical, therefore, that the optimal dose and frequency of BCG immunotherapy be determined while cautiously avoiding excessive BCG administration. Since several biological systems are involved, it is likely that optimal BCG administration will vary from patient to patient. In an effort to develop appropriate monitors of the immune response which may be used to guide effective BCG immunotherapy, we propose to systematically monitor skin test reactivity to PPD, trychophytin, and candida antigens, leukocyte migration and adherence inhibition to bladder tumor and BCG antigens, humoral immunity to bladder tumor and BCG antigens as measured by solid phase radioimmunoassay, serum blocking factors, and serum anti-IgG factors.

238. IMMUNOTHERAPY OF BLADDER CARCINOMA IN MICE

Lamm, D. L., Harris, S. C., Paque, R. E., Thor, D. E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Urology Section, *San Antonio, Texas*, 78284, United States of America

The object of this research is to improve the therapy of bladder carcinoma by evaluating a murine model which closely parallels the human disease. A transplantable chemically induced transitional cell carcinoma (MBT2) is employed and tumor incidence, growth, and animal survival are compared with those of appropriate controls. Tumor transplantation is accomplished by intradermal or subcutaneous inoculation, wound irrigation, or intravesical instillation. Representative results are as follows: 1. Wounds contaminated with MBT2 cells resulted in 100 percent instance of tumor and death in control animals whereas BCG irrigation resulted in 60 percent tumor incidence and death rate (p less than .005, life tables) in BCG preimmunized animals and 30 percent incidence (p is less than .001) in BCG treated animals without prior BCG immunization. Further evaluation of these animals has demonstrated that the resistance to subsequent tumor challenge is of long duration and is statistically significant when compared with that of controls. 2. In an intradermal transplantation model employed to evaluate the role of adjuvant chemoimmunotherapy in bladder cancer, BCG immunotherapy was compared with single and combination chemotherapy resulting, for example, in the following order of effectiveness: BCG plus cytoxin (CY) plus methotrexate (MTX) resulted in a mean log slope tumor growth of .1240; CY plus MTX (.1968), BCG (.2924), cis platinum (.3101), CY (.3356), MTX (.3570), AMSA (.3776), methylgag (.4173), control (.5003), and anthracenedione (.5343). Both of the combination groups had significantly decreased tumor growth and prolonged survival compared with control and single agent therapy groups (p less than .05). Protein A immunoabsorption has identified tumor antigens in MBT2. 3. In other experiments 'immune' RNA did not inhibit tumor growth while levamisole and keyhole-limpet hemocyanin immunotherapy did (p less than .01).

239. IMMUNOTHERAPY OF BLADDER CARCINOMA IN MICE

Lamm, D. L., Thor, D. E., Harris, S. C., Smith, K. O., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Urology Section, *San Antonio, Texas*, 78284, United States of America

OBJECTVES: To correlate cellular and humoral assays of immunity to bladder carcinoma antigens with a course of bladder cancer and to evaluate these as aids to diagnosis and treatment.

PLAN AND METHODOLOGY: Bladder tumor patients are evaluated at presentation and at three month intervals thereafter with leukocyte migration inhibition (LMI) and leukocyte adherence inhibition (LAI) assays of cellular immunity to T24 bladder tumor cell line. Humoral immunity is similarly evaluated using Elisa and RAI. Skin test reactivity to PPD and in vitro immunity to PPD are also performed and assays are correlated with clinical status as documented histologically.

FINDINGS: More than 200 serial assays on 69 bladder tumor patients have confirmed statistically significant (p less than 0.01) correlation of LMI and LAI immunity with the presence of bladder tumor. Using Elisa and RAI assays of humoral immunity to 8 different cultured human bladder tumor cell lines, to date no difference in reactivity among 32 controls, 32 bladder tumor patients with existing tumors, and 32 bladder patients without existing tumors has been found. PCG immunotherapy (NIH funded) has resulted in statistically significant (p equals 0.023) delay of tumor recurrence, and is associated with conversion of PPD skin test, LMI, and RAI responses. Of 5 BCG treated patients with tumor recurrence, 2 remained skin test negative, another 2 were previously skin test positive, 4 had a negative LMI to PPD at the time of tumor recurrence, and 2 had less than 50% increase in BCG antibody titer.

240. IMMUNOTHERAPY OF BLADDER TUMORS IN A RAT MODEL SYSTEM

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The objective of this program is to establish and define a clinically relevant rat bladder tumor model for use in evaluating various immunotherapeutic and immunochemotherapeutic approaches to the treatment of carcinoma of the bladder.

Bladder tumors will be induced in Fischer 344 rats by oral administration of the chemical carcinogen FANFT (N-(5-nitro-2-furyl)-2-thiazolyl)-formamide). The effects of parameters such as exposure interval and dietary lipid content on carcinogenesis will be investigated. Bacillus Calmette Guerin cell walls (BCG-CW), or fractions thereof, will be injected directly into the tumors in an attempt to non-specifically alter the host's immune response to its tumor. The effects of the incorporation of mitomycin C, cis-platins, or other chemotherapeutic agents into this protocol will also be investigated. Parameters of cellular and humoral immunity will be followed. Results of these studies should be directly applicable to the treatment of bladder cancer in humans.

Studies to date have established that 22 weeks of 0.2% FANFT will induce tumors in 100% of the rats, that high dose BCG-CW combined with intravesicle live BCG enhances tumor growth, that repetitive intratumoral injections are more effective than single injections in prolonging host survival, and that adjuvant chemotherapy with mitomycin C does not improve survival. To monitor immune responses to BCG-CW, an agarose microdroplet direct macrophage migration inhibition assay was developed as an in-vitro assay of cellular immunity, an in-vivo delayed cutaneous hypersensitivity assay using footpad and ear testing sites was established, and a solid phase RIA for detecting circulating antibodies to BCG antigens was developed. There was excellent correlation among these assays, suggesting that immunologic responses in subjects receiving non-specific immunostimulation with BCG may be effectively monitored by simple periodic serologic assay for circulating antibody to BCG antigens.

4. RADIOTHERAPY

241. RADIOBIOLOGICAL INVESTIGATIONS OF FRACTIONATION PROBLEMS OF RADIOTHERAPY OF MALIGNANT TUMORS

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Different factors important for radiotherapy are investigated in vitro; for instance the effect of oxygen on the lethal effect of radiation and repair of damage, radiosensitizer and cytostatics used in the clinic. A clinical trial based on these results is proceeding with superfractionated treatment of bladder carcinoma. The clinical results are encouraging.

242. RADIOTHERAPY OF CANCER OF THE BLADDER, BRONCHUS, AND CERVICAL UTERI IN COMBINATION WITH RADIOSENSITIZING DRUGS

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A randomized clinical trial with misonidazole, a drug used for specific radiosensitization of hypoxic cells of tumors, in combination with daily multifraction radiotherapy (DMF) began in 1979 and included patients with 1) transitional bladder carcinoma, stage T3 NX MO, 2) non-oat cell bronchial carcinoma, non-resectable, 3) carcinoma of the cervix uteri, stage III. To test: the local and general tolerance of misonidazole in combination with DMF radiotherapy, particularly neurotoxicity; the immediate response of the tumor, evaluated as tumor mass volume reduction; the length of local tumor control, the quality of life and the survival of patients. For each side, patients were at random assigned to a study or to a control group. Study group patients were administered misonidazole every day, 650-800 mg/sq. m., 3 hours before the first session of radiotherapy, 1Gy 3 times every day with an interval of 4 hours between sessions, for 3-3 1/2 weeks. Control group patients received placebo instead of misonidazole; radiotherapy was administered following the same scheme. On the whole, 20 patients from the study group and 18 from the control group have been evaluated. The local tolerance to radiation treatment alone or in conjunction with misondazole was good, without significant differences between groups. 11/20 patients treated with misonidazole showed toxic symptoms (rash 1 p., oral mucositis 1 p., ototoxicity 1 p., sensorial peripheric neuropathy 6 pts.) which appeared 2-3 weeks after the beginning of treatment and persisted for 4-15 weeks. For all neoplastic sites tumor shrinkage was more frequent and larger in the misonidazole plus RT group than in the placebo plus RT group. A study of drug concentration in blood and in normal and neoplastic tissues in bladder carcinoma patients after total cystectomy has begun.

243. FERMILAB NEUTRON THERAPY FACILITY

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OBJECTIVE: Continue experimenting on the effectiveness of fast neutron beam radiation therapy for controlling selected tumors.

During this fifth year of operations, emphasis will be on increasing protocol patient accrual, the goal being 400 new cases. The following protocols will be used, (1) RTOG approved: carcinoma of the cervix, potentially resectable head and neck carcinomas, nonresectable head and neck carcinomas, malignant gliomas with hypoxic cell sensitizer, adenocarcinoma of the prostate, carcinoma of the bladder, carcinoma of the esophagus, and non-oat cell cancer of the lung, and (2) local, phase II: tumors of salivary gland and pancreas, soft tissue and osteosarcomas, melanomas, and selected adenocarcinomas.

Patients will be randomized into the appropriate arms as defined in the protocols, thus, they will be irradiated with photons alone, photons plus neutrons, photons plus neutron boost to reduced volume, and neutrons only.

The current program of quality control of treatment in the network of referring institutions will be continued and improved as experience is gained in this new type of activity.

Statistical analysis of follow-up data will begin.

244. METHOD FOR PROTECTION FROM RADIATION INJURY

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The primary objective of this program is to minimize or eliminate radiation injury to the small bowel during high dose pelvic irradiation. The effort is specifically directed towards application to preoperative high dose adjuvant irradiation in the treatment of high-stage, non-metastatic bladder cancer. The approach is a method that mechanically displaces the small bowel from the field of irradiation, during the period of radiation delivery.

The proposed method involves the insertion of a inflatable, biologically inert (silastic) space-occupying device into the pelvis and lower abdominal cavity. At the same procedure, urinary diversion would be accomplished with an ileal-loop (high). During a subsequent course of 6000 Mev irradiation, the silastic device would prevent small bowel, cecum, and sigmoid colon from entry into the irradiation field. Following the course of radiotherapy a second operative procedure would be undertaken at which time the device would be removed and cystectomy performed.

5. MULTIMODAL AND BROAD THERAPY PROGRAMS

245. PHASE I TRIAL OF CIS-DIAMINEDICHLOROPLATINUM (NSC 119875) (DDP) COMBINED WITH SMALL FIELD PELVIC RADIATION THERAPY (ABBREV)

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The purpose of this Protocol is to assess the toxicity associated with the concurrent administration of DDP with small field pelvic radiation therapy by external beam. Our hypothesis is that this combined regimen will not have a major complication rate of more than 10%.

The plan is also to evaluate, when possible, therapeutic response and to make assessments of tumor and host characteristics as they relate to tumor response and possible patient toxicity, particularly: (1) To evaluate cystoscopically the response rate of the primary bladder tumor in patients with known visible residual disease. (2) To assess the duration of tumor response

(disease-free interval), pattern of failure, site(s) of recurrence(s) and patient survival. (3) To assess the following parameters that possibly may influence patient tolerance or therapeutic response: (a) histologic type, grade and stage, as well as configuration (papillary, sessile or flat, based on both gross and microscopic findings) of the primary bladder tumor, (b) the presence of demonstrable invasion of lymphatics and/or blood vessels in the primary tumor (elastic tissue stain) and (c) age and sex.

The plan is to register 25 patients. It is anticipated that this pilot study will not give statistically significant information with regard to the primary bladder tumor response rate (local control rate), nor the incidence of the development of distant metastases. However, this pilot study nevertheless is important for documenting that this rational combined regimen is tolerable and clinically acceptable as an approach to patients with invasive primary bladder carcinoma who are unsuitable for cystectomy.

246. DDP WITH SMALL-FIELD PELVIC RADIATION THERAPY FOR PATIENTS WITH LOCALIZED INVASIVE BLADDER CANCER WHO ARE UNSUITABLE FOR CYSTECTOMY

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Protocol 8 of the National Bladder Cancer Collaborative Group A is designed to evaluate the efficacy and toxicity of DDP combined with concurrent administration of small-field pelvic radiation therapy by external beam in patients with clinically localized invasive primary bladder carcinoma who are unsuitable for cystectomy. Patients receive 8 courses of DDP, 70 mg/M2 every three weeks, and 6480 rads given over 7-10 weeks. Patients are evaluated by cystoscopy every 12 weeks, and are followed for five years or until death.

247. COMBINATION CHEMOTHERAPY AND RADIATION THERAPY OF MURINE BLADDER CANCER

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OBJECTIVES: A. To develop an effective regimen of treatment using combinations of cyclophosphamide, cis-diamminedichloroplatinum, and Adriamycin with and without radiotherapy for controlling bladder tumor growth and increasing survival in experimental animals. B. To determine the effectiveness of the tumor specific radiosensitizer, misonidazole, on bladder tumors and develop the most effective treatment schedule using fractionated radiation.

PLAN: Experiments use a leg transplantable model of the N-(4-5-nitro-2-furyl)-2-thiazolyl) formide (FANFT)-induced transitional cell carcinoma of the bladder in C3H-He female mice. Tumors are palpable in 21 days after injections of 5 times 10 to the 4th power cells and treatments begin when tumor diameters reach 6-8 mm. Groups contain 20-30 mice. Drugs are administered i.p.

METHODS: Tumors are maintained by serial transplantation and are stored in liquid nitrogen. Cell suspensions are prepared using double trypsinization for 20 minutes at 37 degrees C and counted with a Coulter counter. Viability is determined by trypsin blue exclusion.

FINDINGS: A. Combinations of cis-diamminedichloroplatinum and cyclophosphamide prevent tumor growth and significantly increase survival, but 5 repeated weekly doses appear to be toxic. Current studies involved smaller doses and longer time intervals between treatments. B. The most effective regime thus far obtained is misonidazole given 45 minutes prior to 600 rads, and this treatment repeated 5 times over 10 days. This provides a significant increase in survival time and slows tumor growth when compared to both untreated controls and radiation alone.

CLINICAL RELATIONSHIPS: This model provides a good correlation to clinical bladder carcinoma and these studies therefore relate directly to possible treatments for bladder cancer patients.

248. TOPICAL ADRIAMYCIN/BLADDER HYPERTHERMIA VS TOPICAL ADRIAMYCIN IN TREATMENT OF STAGE 0 PAPILLARY TRANSITIONAL CELL CARCINOMA OF BLADDER

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OBJECTIVES: To evaluate the combination of topical bladder adriamycin and topical bladder hyperthermia in the eradication of superficial noninvasive papillary bladder cancer.

PLAN: Forty patients with recurrent papillary stage 0 tumors will be randomized to topical adriamycin with or without concomitant bladder hyperthermia.

METHOD: Continuous pump irrigation of the bladder for 4 hours will be performed at 38 degrees C or 45 degrees C with adriamycin 100 mg/2 liters.

249. ADJUVANT CHEMOTHERAPY WITH CIS-PLATINUM AFTER PREOPERATIVE RADIATION THERAPY OF THE URINARY BLADDER (ABBREV)

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This protocol is designed to determine if treatment with 4000R of radiation and immediate cystectomy followed by cis-platinum will improve patient survival in comparison to the rate of patient survival following treatment with radiation and cystectomy but no adjuvant chemotherapy. This is Protocol 7 of the National Bladder Cancer Collaborative Group-A multi-institutional study. As of October 1, 1979, 43 patients have been accrued from the ten institutions across the country, six of whom are from the UT-VAH complex. Three of these patients have had cis-platinum initiated. It is too early to have any significant data on this protocol at this time.

250. ADRIAMYCIN HYPOGASTRIC ARTERY INFUSION/ BLADDER HYPERTHERMIA THERAPY FOR TRANSITIONAL CELL CARCINOMA OF THE BLADDER

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OBJECTIVE: To evaluate the toxicity and efficacy of the combined modalities, Adriamycin hypogastric artery perfusion/ bladder hyperthermia, in the irradication or down-staging of bulky transitional cell carcinoma limited to the pelvis.

METHOD: Infusion of Adriamycin over 48 hours via percutaneously placed hypogastric artery catheters with concomitant and post-perfusion heating of the bladder (96 hours). Adriamycin dosage and bladder temperature being escalated every 3rd patient. Cystectomy performed on day 21.

RESULTS: Six patients have completed protocol. Local tumor effects seen include extensive necrosis of primary and metastatic lymph nodes. Toxicity has included only 1 patient with leukopenia. Two patients died of metastatic disease at 4 and 6 months. Two are NED at 5 and 9 months, two are alive with metastatic disease at 1 and 5 months postoperative.

PLAN: Continuation of Phase I study, then Phase II trial.

251. IMMUNOTHERAPY AND CHEMOIMMUNOTHERAPY OF THE FANFT TUMOR

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The FANFT-induced murine bladder tumor has become an important model for the study of human bladder cancer, and recent experiments in our laboratory have demonstrated responsiveness of the tumor to immunotherapy and to chemoimmunotherapy. We will first study the relationship between the location of the tumor and the site of BCG injection. We will inject it in the groin above the site of the tumor. Second, chemoimmunotherapy of the FANFT tumor with Cytoxan and C. parvum will be studied in hopes of finding the optimum treatment schedule and dose in an attempt to produce complete tumor regression. Third, we propose a) to determine dose-response relationships of I-RNA in animals with growing FANFT

tumors, and b) to assess the effect on growing FANFT tumors of I-RNA combined with chemothrapy, non-specific immunotherapy and tumor antigen. Fourth, we will measure the antitumor antibody levels in mice with growing FANFT tumors as influenced by the various treatment modalities. An attempt will be made to correlate changes in tumor growth secondary to therapy with changes in antibody levels.

252. BLADDER CANCER - PREOPERATIVE IRRADIATION, CYTOSTATICS AND SURGERY

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OBJECTIVE: To increase survival in patients with bladder cancer classified as: T1N0M0 (A); T2N0M0 (B); T3N0M0 (B2C); T2N1M0 - T2N2M0; T3N1M0 - T3N2M0.

METHOD: Preoperative irradiation and cytostatics (thiophosphoramide and 5-fluorouracil). Surgery: electrocoagulation, transurethral resection, partial cystectomy, total cystectomy with or without regional ganglionar dissection.

253. ADJUVANT RADIATION THERAPY FOR OPERABLE BLADDER CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

254. INHIBITION OF TUMOR PROMOTION BY PROTEASE INHIBITORS

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Our observation that protease inhibitors block tumor promotion has grown into a tool for chemoprevention of cancer. The work of the last two years demonstrates that diets containing soybeans delay the onset of two-state carcinogenesis using nitroquinoline oxide as the initiator and PMA as the promoter: delays and diminishes breast tumor response in Sprague-Dawley rats treated with X-rays and delays changes in the bladder epithelium caused by the bladder carcinogen FANFT in Fischer rats. We plan to confirm in this year's work that, indeed, a protease inhibitor is responsible for the apparent prevention of cancer. We failed to get a precipitating antibody by injection of purified Kunitz soybean trypsin in foot pads of rabbits. To confirm the appearance of soybean trypsin inhibitor (SBTI) in the tissues where tumors are observed, we will prepare radioactive soybean trypsin inhibitor by introducing the tritium or iodine into SBTI. We will test if smaller units of the inhibitors are still capable of inhibiting proteases. We plan to digest purified soybean trypsin inhibitors and soybean with pepsin at pH2 and isolate new inhibitors formed by affinity chromatography using trypsin and chymotrypsin Sephadex columns. Using radioactive SBTI as the source material, we hope to identify smaller units of the soybean trypsin inhibitor. We will look for such fragments in skin and breast tissue.

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255. CHEMOPREVENTION OF EPITHELIAL CANCER BY RETINOIDS

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The basic objective of these efforts is the evaluation of the efficacy of retinoids of differing chemical structures in preventing the development of epithelial cancer during its preneoplastic period. A number of target sites for such chemoprevention are anticipated: respiratory tract, urinary bladder, breast, and colon. Appropriate animal models are currently available in the literature for these organ sites. Carcinogens and retinoids necessary for these studies will be provided in most instances by the National Cancer Institute as available and in accordance with program priorities. Close coordination and mutual consultation by contractor and the NCI is expected in reaching the objectives of this contract.

256. INHIBITION OF BLADDER TUMORS IN RATS WITH RETINOIDS

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Bladder cancer in man continues to be a problem of major importance. The development of several animal models for human disease, which is primarily a transitional cell carcinoma, has permitted intensive studies of aspects which might be of use in prevention of bladder cancer. Recent studies have shown that a synthetic analog of vitamin A (retinoids) may be used to prevent epithelial cancer of the skin, respiratory tract and mammary gland in experimental animals.

At present, the work is in progress to develop animal models and use 13 cisretinoic acid as a preventive agent in the prevention and/or inhibition of chemically induced bladder tumors in rats.

Methyl-nitrosourea produces bladder tumors on intravesical instillation. Histologically the tumors are transitional cell as well as squamous cell carcinomas.

257. PREVENTION OF FANFT URINARY BLADDER TUMORIGENESIS

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The overall objectives of this project are to study the mechanisms by which carcinogens induce bladder cancer and to study factors which may intervene in these mechanisms to prevent such cancers. The interaction of N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide (FANFT), labeled by conjugation with an azo dye, with DNA and polynucleotides will be studied in vitro. The effects of allopurinol and 2,5-di-O-acetylglucosaccharo-(1, 4) (6, 3)-dilactone on the carcinogenicity of N-butyl-N-(4-hydroxybutyl) nitrosamine will be evaluated. The influence of these two compounds on tissue distribution and macromolecular binding of (14C) FANFT in rats will be determined. Rats will be fed uracil to produce urinary stones, and the effect of these stones on the induction of bladder cancer by FANFT will be ascertained. Harmane, an element of charred meat and a known comutagen, is thought to be a metabolite of tryptophan. Harmane's ability to promote bladder carcinogenesis will be studied. Two mutagenic hydroxamic acids, 2-naphthohydroxamic acids and benzoylaminoacetohydroxamic acid, will be fed to rats to assess their carcinogenicity. Finally, a series of polyphenolic compounds will be tested for mutagenicity. These studies may have relevance to the prevention of human bladder cancers in that they will contribute to the understanding of bladder tumorigenesis in experimental animals and in the identification of environmental carcinogens.

258. INHIBITION OF URINARY BLADDER CARCINOGENSIS BY 2-HYDROXY ETHYL RETINAMIDE

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The objectives of this project are to confirm and expand the evidence for inhibition of N-Butyl-N-(4 Hydroxybutyl)-nitrosamine (OH=BNN) induced urinary bladder carcinogenesis in Fischer 344 rats with 2-Hydroxyethyl retinamide (2-HER) and to study the chronic toxicity of the retinamide. To realize these objectives, experiments are being conducted to investigate the following: 1. Assess the degree of toxicity and bioaccumulation of 2-HER anti-neoplastic and higher doses. 2. Through sequential and long-term observations, determine if 2-HER influences the biological behavior of pre-neoplastic and neoplastic lesions. 3. Compare the efficiency of 2-HER urinary bladder tumor inhibition when administered before rather than after exposure to the carcinogen, i.e., by an effect on initiation as well

as on promotion or progression. 4. Determine if 2-HER affects carcinogen induced macromolecular synthesis in the urothelium at various stages in the carcinogenic process.

The toxicity experiment compares the effects of lifetime feeding of 0 to 5.0 mM of 2-HER/kg of diet. Body weights, food intake, toxicological, biochemical and pathological parameters will be evaluated. The carcinogenesis study includes groups of 85 rats each getting 1.5 mM 2-HER/kg of food. Sequential sacrifices with pathological examinations, including scoring of urinary bladder lesions, are done. Experiments measuring possible urothelium DNA, RNA, and protein synthesis changes will utilize 3H-thymidine, 3H-orotic acid, and 3H-leucine isotope labelling, respectively. Transplantation studies will involve retinoid versus non-retinoid syngeneic recipients.

259. CLINICAL ONCOLOGY (MULTIDISCIPLINARY)

Carbone, P. P., University of Wisconsin, Madison Campus, Center for the Health Sciences, Dept. of Human Oncology, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

Projects included in this program focus on the natural history, causation, detection, and experimental treatment of solid tumors, stressing use of chemotherapeutic drugs and modulators of the immune and endocrine systems. Clinical trials for breast and pancreatic tumors; causation, early detection and intravesical treatment of bladder tumors; analysis of bony metastasis and hypercalcemia in breast and prostate cancers; in vitro and clinical immunological effects of levamisole and interferon; and pharmacology and clinical efficacy of platinum-containing coordination compounds and antiestrogens comprise studies under way.

The program depends on interdisciplinary collaboration of laboratory and clinical investigators, biostatisticians, and data management experts devoted to an integrated, interactive effort.

BIBLIOGRAPHIC REFERENCES: Tormey, D.C., and Carbone, P.P. What is the optimum number of agents? Int. J. Radiation Oncology Biol. Phys. 4: 301-303, 1978. Davis, T.E., and Carbone, P.P. Drug treatment of breast cancer. Drugs 16: 441-464, 1978.

260. EVALUATION AND MANAGEMENT OF BLADDER CANCER

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The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

261. UNIVERSITY ONCOLOGY PROGRAM

Bagshaw, M. A., Rosenberg, S. A., Martinez, A., Coleman, C. N., Jacobs, C., Kempson, R., Fee, W., Stockdale, F., Sikic, B., Stanford University, School of Medicine, Dept. of Radiology, *300 Pasteur Dr., Stanford, California*, 94305, United States of America

This proposal is for the continuation of Stanford participation in the Northern California Oncology Group (NCOG) for a multi-institutional cooperative study of the multi-modality treatment of a variety of neoplasms. The multi-modality studies will include various combinations of surgery, radiation therapy, and chemotherapy, used either as adjuvants or as primary treatment in carcinoma of the breast, bronchus, gastrointestinal tract, urinary bladder, prostate, non-seminoma-testicular neoplasms, ovarian carcinoma, cervical carcinoma, endometrial carcinoma, epidermoid carcinoma of the head and neck and melanoma. Stanford intends to participate in almost all of the active programs which, it is estimated, will number about 30 at any given time. Special features of the Stanford participation will include an extramural network of participating medical oncologists, the use of our oncology day care center for the administration of chemotherapeutic agents on an out-patient basis and the use of our clinical research center (CRC) for in-patient hospitalization in support of protocols approved by the CRC advisory board. In addition to clinical participation Stanford intends to use its radiobiology facilities for further studying radiotherapeutic and chemotherapeutic interactions, hyperthermia, and radiation sensitizers.

262. BLADDER CANCER MODEL - AID FOR PLANNING AND EVALUATION

Greenfield, R. E., Ellwein, L. B., Hilgar, A. G., Friedell, G. H., St. Vincent Hospital, Dept. of Pathology, *25 Winthrop St., Worcester, Massachusetts*, 01604, United States of America

This research grant application proposes a collaborative effort between the Headquarters Staff of the National Bladder Cancer Project and Dr. Leon B. Ellwein of Science Applications, Incorporated, to further refine and test a computerized model of bladder cancer designed for use as a tool in research planning and evaluation of progress and to develop methods for the measurement of the quality of life in patients under treatment for cancer of the bladder.

The bladder cancer model will serve as a mechanism for conducting active planning for research, defining what studies should be undertaken and how, and providing a framework for evaluating the logic and consistency of concepts and hypotheses.

The question being tested is whether methods of evaluation that have been successfully employed in other complex decision-making situations involving uncertainty and individual preferences can be gainfully applied in the area of bladder cancer research.

B. WILMS' TUMOR

263. DERMATOGLYPHICS IN CHILDHOOD NEOPLASIA

Oorthuys, A. M., deVaan, G. A., Haanen, C. A., Katholieke Universiteit Nijmegen, Dept. of Human Genetics, *Erasmuslaan 4, Nijmegen, Netherlands*

OBJECTIVE: To characterize flexion creases and dermal configurations on palms and soles of patients with childhood neoplasia and of their first degree relatives.

APPROACH: Printing of palms and soles of pediatric patients with acute leukemia (AL) or with other neoplasms (malignant non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, brain tumors, Hodgkin's disease) and their relatives.

PROGRESS: Material has been extensively enlarged; results remain consistent with earlier reports. Association between resistance to childhood neoplasia and early fetal development is feasible in so far that among young patients with AL a relation seems to exist between good prognosis and absence of variant dermatoglyphic features. Correlation of dermatoglyphic variance, defects of purine- and pyrimidine-metabolism, and HLA-typing, among patients with childhood neoplasia and their relatives, is the objective of further study.

264. SISTER CHROMATID EXCHANGE (SCE) IN CHILDREN WITH A MALIGNANT DISORDER

Seshadri, R., Sutherland, G., Flinders University of South Australia, Flinders Medical Centre, Dept. of Haematology, *Bedford Park, S Australia 5042, Australia*

OBJECTIVE: 1. To analyze SCE rate in the lymphocytes of children with cancer and their relatives at the time of diagnosis. 2. To analyze SCE rate in children who have been treated with cancer chemotherapeutic agents.

APPROACH: Peripheral blood lymphocytes are cultured in the presence of bromodeoxyuridine for 3 days and SCE rate in the chromosome is analyzed.

PROGRESS: To date 40 children with various forms of malignancy have been analyzed. Children with Wilms' tumor who have been treated with actinomycin showed increased SCE rate compared to controls. No specific abnormality as yet has been found in newly diagnosed cases.

265. THE USE OF A FOUR-DRUG COMBINATION CHEMOTHERAPY REGIME (DAVE) IN THE TREATMENT OF ADVANCED WILMS' TUMOR

Malpas, J. S., Graham Pole, J. R., Dunger, D. B., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A four-drug combination using dactinomycin, adriamycin, vincristine and endoxan (cyclophosphamide) together with surgery and irradiation was used in the treatment of stage III and stage IV Wilms' tumor with undifferentiated histology. Eighty percent of children in the study group achieved a complete response. Of these children who achieved a complete response the median survival time has not yet been reached, but must be in excess of 3 1/2 years. Toxicity has not been a problem with the drug combination used. Histology and site of metastases have been important prognostic factors.

266. CANCER AND LEUKEMIA GROUP B - RADIOTHERAPY

Glicksman, A. S., Reinstein, L. E., Tefft, M., McShan, D., Rhode Island Hospital, *593 Eddy St., Providence, Rhode Island*, 02903, United States of America

This is a request for supplemental funding so that the Radiotherapy Office of the CALGB through its Quality Assurance Program can undertake the quality assurance of two Pediatric Intergroup Studies, the Intergroup Rhabdomyosarcoma Study-2 and the National Wilm's Tumor Study-3. Dr. Melvin Tefft is the radiotherapy representative of the CALGB to both of these studies and is a member of the CALGB Quality Assurance Overseers Committee. The intent at this time is to utilize the organization, procedures, and overall facilities of the CALGB Quality Assurance Program for the two Intergroup Pediatric Studies rather than to establish free-standing, independent, quality assurance programs for IRS-2 and NWTS-3.

267. NUTRITION SUPPORT OF CHILDREN WITH WILMS' TUMORS

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The early diagnosis and multimodal treatment of children with Wilms' tumors have vastly improved survival rates. However, severe malnutrition (PEM) and numerous complications and toxicity are often associated with the treatment. Malnutrition reduces the capacity to withstand aggressive treatment, increases susceptibility to opportunistic infections, depresses immune function and increases morbidity and mortality. The purpose of this study is to prospectively evaluate the benefits and complications of several modes of nutrition support (i.e., enteral nutrition, partial parenteral nutrition - PPN, peripheral nutrient infusion with enteral nutrition - and total parenteral nutrition - TPN, central nutrient infusion) in children (ages one to seven years) receiving multimodal treatment for Wilms' tumors, stages II-IV. Each regimen will be evaluated for its effectiveness in preventing or reversing PEM, maintaining or restoring immune competence, and obviating treatment modifications and complications. Children with stage II-IV Wilms' tumors who are considered malnourished at diagnosis will be randomized to receive either TPN or PPN throughout the period of irradiation. Nourished children with either stage IV or stage II/III and unfavorable histology Wilms' tumors will be randomized to receive either PPN or TPN throughout the six weeks of abdominal irradiation. Nourished children with stage II/III and favorable histology Wilms' tumors will receive either a comprehensive enteral nutrition program or PPN throughout the four weeks of intense treatment which includes abdominal irradiation. Thereafter, all children will receive a comprehensive enteral nutrition program to prevent subclinical PEM during 2, 3, or 4 drug chemotherapy maintenance programs. Nutritional state, immunological capacity, treatment modifications and complications will be evaluated at diagnosis and at 4, 6, 19, and 26 weeks during the initial, intense and maintenance periods.

268. TREATMENT OF CHILDHOOD CANCER

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The current success in treating a number of types of childhood cancer is the result, in large part, of therapeutic research conducted by the cooperative pediatric cancer groups. Because most childhood cancers are rare, it is only through this mechanism that adequate numbers of patients can be accrued in reasonable lengths of time and that therapeutic questions can be answered. We will participate in the pediatric division of the Southwest Oncology Group (SWOG) so that our patient population can be used to answer treatment questions which would be impossible to answer were we to conduct only single institution studies.

There are some pediatric solid tumors for which the accrual, even in cooperative groups, is insufficient for meaningful therapeutic studies to be conducted. However, a number of intergroup studies are presently active and we plan to participate in these studies through the pediatric division of SWOG. Specifically, we will continue to enter patients on the National Wilms' Tumor Study, the Intergroup Ewing's Sarcoma Study, the Intergroup Rhabdomyosarcoma Study and the Intergroup Hodgkin's Disease Study. The diseases included in these intergroup studies are those which most commonly demand an interdisciplinary approach. We are strongly committed to this approach and have a good working relationship with the necessary cooperating specialities, including Radiation Therapy, Pediatric Surgery, Neurosurgery and Orthopedic Surgery.

As more children enter long-term remissions from their diseases, the identification, treatment and potential for prevention of complications of therapy have become significant areas for research. Our major areas of investigation include population based studies of major complications of radiation therapy and chemotherapy, investigations into the treatment and prevention of varicella-zoster infection in immunosuppressed patients and evaluation of the acute and long-term effects of radiation therapy and chemotherapy on various committed stem cell pools and the peripheral blood and bone marrows.

269. CHILDREN'S CANCER STUDY GROUP

Miller, D. R., Steinherz, P. G., Allen, J. C., Tan, C., Memorial Hospital for Cancer & Allied Diseases, Dept. of Pediatrics, *1275 York Ave., New York, New York*, 10021, United States of America

The Children's Cancer Study Group is a multidisciplinary cooperative group of investigators from 26 institutions in the United States and Canada collaborating in the development, implementation and completion of prospective, randomized clinical trials in pediatric hematologic malignancies and solid tumors, including acute lymphoblastic leukemia (ALL), acute nonlymphoblastic leukemia (ANLL), brain tumors, lymphomas (non-Hodgkin's and Hodgkin's), Wilms' tumor, neuroblastoma, rhabdomyosarcoma, bone tumors, hepatoblastoma, 'histiocytosis X', and retinoblastoma. Natural history, biologic characterization of cancer (pathology, immunology, biochemistry), prognostic factors, late effects and supportive care aspects are also stressed in these studies involving pediatric oncohematologists, surgeons, pathologists, diagnostic and therapeutic radiologists, neurologists, psychiatrists, psychologists, cell biologists, immunologists, and infectious disease specialists. New agent Phase II trials for patients failing initial therapy and new modalities of therapy, including bone marrow transplantation, are additional major thrusts of the cooperative group. MSKCC - NYH-CMC (and its affiliates) has been a major contributor to the efforts of the Group. This research proposal outlines the center's participation in present and future CCSG endeavors at the executive level as well as in the development of new pilot studies for eventual groupwide participation.

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270. CHILDREN'S CANCER STUDY GROUP

Tubergen, D. G., Favara, B., Chang, J., Daniel, W., Odom, L., Heideman, R., Children's Hospital, Dept. of Oncology & Hematology, *1056 E. 19th Ave., Denver, Colorado*, 80218, United States of America

Children's Cancer Study Group is engaged in conducting clinical research programs which have been developed to improve the care and survival of children with malignant disease. This is accomplished by means of treatment protocols conducted on a limited institution (pilot) basis, groupwide studies, and intergroup studies (such as Wilms' tumor, Hodgkin's disease and rhabdomyosarcoma studies).

The Oncology Center personnel at The Children's Hospital will participate in the design and execution of all such protocols. We will provide to the Group a well-established multidisciplinary team with a well-organized data collecting system. Our research capability will permit us to participate in cell surface marker studies on a local basis only or as a limited reference source. Local protocols conducted over the past three years may provide useful information for new protocol design within the group.

271. CHILDREN'S CANCER STUDY GROUP

Chard, R. L., Johnson, F. L., Pendergrass, T. W., Children's Orthopedic Hospital & Medical Center, Division of Hematology-Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

This proposal is for continuation of research into the natural history, treatment and epidemiology of the statistical conduct, design, collation, and publication of childhood cancer. It will continue to emphasize multimodal aspects of the Children's Cancer Study Group which has realized such excellent results in the past in Wilms' tumors and rhabdomyosarcoma and has now helped in defining acute childhood lymphocytic leukemia as more than one disease entity which requires different treatments for different groups. Also, treatment has been improved in osteogenic sarcoma and Ewing's sarcoma and, though advances are more meager, there have also been statistical improvements in survival of neuroblastoma patients. Childhood nonlymphocytic leukemia patients have also shown improved survival and the Children's Cancer Study Group has now combined in a Groupwide study to compare bone marrow transplantation in first remission to more standard conventional chemotherapy in a controlled fashion.

During the period from November, 1976 to December, 1979, 389 children with childhood cancer were seen at this institution; 182 with leukemia, 148 who were treated on study, 44 who were not on study, and 207 children with solid tumors. We have been a member of the Children's Cancer Study Group since 1959 and strong permanent referral patterns have been established. It is therefore anticipated that the patient load will continue to be stabilized and slightly increased over the next several years. A close working relationship with the adult leukemia center under Dr. E. Donnall Thomas at the Fred Hutchinson Cancer Research Center continues. This includes the exchange of professional personnel on the Fellowship level. Forty-three bone marrow transplantations on children with acute leukemia have been done at this institution from 11/1/76 to 12/1/79. Collaborative studies continue in immunology with the Fred Hutchinson Cancer Research Center, primarily through the efforts of Irwin D. Bernstein, M.D.

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272. CHILDREN'S CANCER STUDY GROUP

Heyn, R. M., Holland, R., Hutchinson, R., Ertel, I., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Pediatrics & Communicable Diseases, *1335 E. Catherine St., Ann Arbor, Michigan,* 48104, United States of America

The proposed and ongoing studies included in this application deal with the treatment of acute leukemia and solid tumors in children. The present new patient study for acute lymphocytic leukemia divides patients by age, WBC at diagnosis, cell morphology, and the status of the CSF at diagnosis. Induction treatment is similar for all groups. Maintenance therapy is randomized within each group to two or more programs for both the CNS and systemic therapy.

New patient therapy for acute non-lymphocytic leukemia includes induction with cytosine arabinoside and adriamycin. Children who enter remission will receive bone marrow transplant if a suitable sib donor is available. All others will continue on multi-drug maintenance therapy.

New solid tumor studies effected within the past year include those in Wilms' tumor, Ewing's sarcoma and rhabdomyosarcoma. All of them are intergroup studies.

New agents in Phase II study of leukemia and/or solid tumors include azapicyl, beta-deoxythioguanosine, prednimustine, Poly I:Poly C, and dianhydrogalactitol.

Interferon is being studied in a controlled trial for the treatment of varicella in children on chemotherapy.

BIBLIOGRAPHIC REFERENCES: Heidelberger, K.P., Schnitzer, B., Tilford, D., Poznanski, A.K., and Heyn, R. Marked skeletal involvement in sinus histiocytosis with massive lymphadenopathy. Accepted for publication in Skeletal Radiology, May, 1979. Lahey, M.E., Heyn, R.M., Newton, W.A. Jr., Shore, N., Smith, W.B., Leikin, S., and Hammond, D. Histiocytosis X: Clinical trial of Chlorambucil. A report from Children's Cancer Study Group. Accepted for publication in Medical and Pediatric Oncology, 1979.

273. CHILDREN'S CANCER STUDY GROUP

Newton, W. A., Miser, A., Miser, J., Distelhorst, C., Mulne, L., Rothermel, K., Boles, E. T., King, D., Clatworthy, H. W., Children's Hospital, Dept. of Pathology/Pediatrics, *561 S. 17th St., Livingston Pike, Columbus, Ohio,* 43205, United States of America

This is a continuation of a cooperative inter-institutional study of cancer in children, utilizing multi-disciplinary approach to treatment of those types of cancer which are suited for scientific analysis in a reasonable period of time. The studies are designed to provide answers to questions concerning optimum management, and at the same time provide the individual institutions with the added strengths to supply their communities with a referral center for childhood cancer.

At the time of writing, there are 11 active protocols dealing with leukemia and 27 dealing with solid tumors, including Phase II studies. The principal protocol for ALL/AML is designed to determine the relative importance of front-end factors in prognosis, with randomized increased therapy during maintenance for those with known poor prognostic findings. The present AML protocol is an effort to improve survival and duration of remission in childhood AML by combining the two best therapies from CCSG 241 and CCSG 102.

Specific protocols currently being used are those for neuroblastoma, Stage III and IV; histiocytosis; retinoblastoma, unilateral and extraocular; brain tumors; osteogenic sarcoma; non-Hodgkin's lymphoma and ovarian tumors. On an intergroup basis, there are active protocols for rhabdomyosarcoma, Ewing's tumor both non-metastatic and metastatic, Hodgkin's disease and Wilms' tumor. Protocols being formulated and finalized are for bilateral retinoblastoma, brain tumors, nasopharyngeal carcinoma, and hepatoma.

In addition, ongoing Phase II protocols utilize a succession or combination of new therapeutic agents such as Vindesine, galactitol, Azapicyl, Prednimustine, beta-TGdR, cis-platinum, Poly I:Poly C and hexamethylmelamine.

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274. SOUTHWEST ONCOLOGY GROUP, PEDIATRIC DIVISION

Pullen, D. J., Miller, R. C., Hickman, B. T., Johnson, W. W., Iyer, R. V., Jackson, J. F., Routh, A., University of Mississippi, Medical Center, School of Medicine, Dept. of Pediatrics, *2500 N. State St., Jackson, Mississippi,* 39216, United States of America

The University of Mississippi Medical Center (U.M.C.) Department of Pediatrics has participated in the treatment protocols and activities of the Southwest Oncology Group (SWOG) since July 1970. In addition to the U.M.C. Division of Pediatric Oncology, the disciplines of pediatric surgery, pediatric pathol-

ogy and radiation therapy are active participants in the program, as are supportive specialties including pediatric radiology, immunology and medical genetics.

The Southwest Oncology Group Pediatric Divisions' central objective is the delineation of increasingly effective means for treating various types of childhood malignancies utilizing the combined efforts of the participating institutions in protocol design and implementation. These collaborative studies form the basis of the U.M.C. Department of Pediatrics' clinical research program in oncology. Studies are currently in progress for acute lymphocytic leukemia, acute granulocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, histiocytosis X, Wilms' tumor, neuroblastoma, rhabdomyosarcoma, osteogenic sarcoma, Ewing's sarcoma, brain tumor and malignant teratoma.

In addition to participating in the SWOG clinical research studies, the U.M.C. disciplines are active in committee functions and protocol development. The U.M.C. Department of Pediatrics is serving as the coordinating institution for the SWOG ALinC 13 pilot and final classification and treatment protocols. ALinC 13 will be the next SWOG pediatric front-line study for acute lymphocytic leukemia.

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275. NATIONAL WILMS' TUMOR STUDY

D'Angio, G. J., Evans, A. E., Breslow, N., Beckwith, J. B., Tefft, M., American Academy of Pediatrics, *1801 Hinman Ave., Evanston, Illinois*, 60204, United States of America

Modern treatment methods have led to a major improvement in the survival rate of children with Wilms' tumor. Combined therapy using surgery, radiation therapy, and chemotherapy now cures more than 85% of patients. However, the outlook is poor for those with unfavorable histology and metastases at diagnosis (about 50% survival). More effective means of treating these patients must be developed. At the same time, all treatments have their risks and complications, and refinements of therapy for those with a good prognosis are needed so as to achieve maximum surivval with the least morbidity. NWTS-1 is now complete, and its primary and secondary objectives have been achieved. 'Natural history' and epidemiologic information has been reported. Gross and microscopic features associated with an unfavorable outlook have been identified. Combined therapy using actinomycin-D (AMD) and vincristine (VCR) is superior to the use of either agent alone. Routine radiation therapy (RT) is not needed in all children with early stage disease. Review of RT given children with more advanced stages, however, left to be defined its role in the modern management of these patients. NWTS-2 is now in the stage of data analysis. Preliminary results suggest that 6 months of AMD and VCR maintenance therapy is satisfactory for Group I children, none of whom receives RT, and that the addition of adriamycin to AMD and VCR gives better results than the use of the two latter alone. NWTS-3 will build on the first two studies and use the staging system developed therefrom. The questions presently planned are: (1) Is two months of AMD and VCR maintenance therapy enough for Stage I? (2) Is RT needed for Stage II? (3) Does 1000 rad suffice for the treatment of Stage III? (4) Can a better drug regimen be devised for Stage IV and unfavorable histology? (5) What are the late adversities of successful treatment in NWTS patients?

276. NATIONAL WILMS' TUMOR STUDY - FAMILY HISTORY

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The National Wilms' Tumor Study is a randomized clinical trial testing various treatment regimens in children. In connection with the trial a questionnaire eliciting information regarding family history is obtained for patients registered in the study.

277. EPIDEMIOLOGY OF MALIGNANT TUMORS IN CHILDHOOD - PROGNOSIS OF WILMS' TUMOUR

Erdoes, Z., Semmelweis Orvostudomanyi Egyetem, Dept. of Paediatrics, *Ulloi Utca 26, Budapest, Hungary*

The frequency of malignant neoplasms, especially Wilms' tumour, has been followed since 1947 in the First Dept. of Paediatrics of the Semmelweis Medical School, Budapest. No increase in the number of malignant tumours was found, a finding consistent with data from other countries. In this period, considerable improvement in the prognosis of Wilms' tumour, recovery in 50-70 percent of the cases has been noted; one patient with cured Wilms' tumour has been followed up for 36 years. Observations continue. Over the next 2 years it is intended to record the exact geographical sites where children with cancer are found. In adults it has been found that the highest frequency in Hungary occurs in the regions bordering on Austria. In the Transdanubian region in Hungary the number of cancer cases on the southern shore of the Lake Balaton is higher than in other parts of the country; the highest frequency of Down's Syndrome was also noted in this region.

C. OTHER RENAL AND UROLOGICAL NEOPLASMS

1. DIAGNOSIS AND PROGNOSIS

278. TUMOR ANTIGENS AND ANALYSIS OF THE IMMUNE RESPONSE

Fossati, G., Della Porta, G., Canevari, S., Lombardi, L., Pierotti, M., Miotti, S., Istituto Nazionale per lo Studio e la Cura dei Tumori, Divisione di Oncologia Sperimentale A, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: To isolate and characterize tumor associated antigens from surgical specimens of tumoral tissues of different histologic type. The antigenicity of various extracts will be assayed by tests of cellular immunity.

APPROACH: KCl extracts from surgical specimens will be further purified by ultracentrifugal flotation on KBr, gel-filtration and affinity chromatography. The different extracts will be analyzed by gel electrophoresis in polyacrylamide. The immunogenicity and the specificity of the extracts will be assayed by delayed cutaneous hypersensitivity reaction (DCHR) and by two in vitro tests of cellular immunity (LAI and LMI).

PROGRESS: Removal of lipoproteins, HLA and human serum albumin from a negative KCl extract of kidney carcinoma gave a steady increase in positive DCHR. This reactivity seemed to have a certain degree of tumor and histologically associated specificity. Further study performed in melanoma patients did not confirm the results obtained in kidney cancer. In fact we observed an increase in frequency of reactivity with purification but this reactivity seemed not to be histologically associated. In addition a variability in the reactivity was observed among different melanoma extracts.

279. EVALUATION AND ANALYSIS OF CIRCULATING IMMUNE COMPLEXES IN NEOPLASTIC PATIENTS

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Circulating immune complexes (CIC) are found in high concentration in the serum of patients with collagen, kidney and liver diseases. Several reports have shown that also in several tumor and leukemia patients CIC levels are abnormally elevated. The present project tackles the question in a broad manner, in its methodological, epidemiological and analytical aspects. First, our methodological approach is based on the observation that no single available method for the detection of CIC can assess all complexes because each method sees a different aspect of the complex and complexes are qualitatively different in different pathological situations. In consequence, we have developed a new method where several recognition units can be utilized. An enzyme-anti-enzyme complex (probe) competes with the CIC for binding sites in the recognition unit (conglutinin, C1q or rheumatoid factor) and the end-point is a reading of bound enzyme activity. This method is presently being used on a medium scale and its results are being critically evaluated. Second, a certain number of homogeneous groups of patients

are selected and CIC determinations are performed (together with the monitoring of a number of immunological parameters such as serum complement levels, lymphocyte stimulability by mitogens, efficiency of NK cells) in close cooperation with clinical teams in the Genoa and Pisa area. The selected groups are: a) lung carcinoma (a follow-up of operated patients with randomized treatments has been set up); b) intestinal tumors; c) lymphomas (Hodgkin's and non-Hodgkin's); d) leukemias; e) African nasopharyngeal carcinoma positive for Epstein-Barr virus (EBV).

Third, the analysis of CIC will be done after isolation from large batches of high titered serum. The antibody and antigen will be studied separately; the latter will be tested for the presence of MHC products and for tumor specific viral antigens or virus-determined cellular antigens (as in the typical case of nasopharyngeal carcinoma complexes). Eventually both isolated ab and antigen moieties may be utilized as specific reagents.

280. HUMAN CANCER SEROLOGY

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The two objectives of the Human Cancer Serology Program are as follows: I. Serological definition and biochemical characterization of distinctive cell surface antigens of human cancer. II. Immunovirologic analysis and biochemical characterization of human cancers of suspected viral etiology. The proposed studies relate to two central questions concerning human cancer: Do human tumor-specific antigens exist and do viruses play a role in the etiology of human cancer? The technique of autologous typing of malignant cells will be used to analyze cell surface antigens of malignant melanoma, renal cancer, astrocytoma, leukemia, lymphoma, and ovarian cancer, and will be applied to breast, lung, and colon cancer as improved methods for the in vitro propagation of these cancers are developed. Serological definition of tumor-specific cell surface antigens of human cancer will be followed by: a) Genetic analysis to determine the chromosomal loci specifying these antigens, b) search for natural antibody to these antigens in the normal human population, c) biochemical characterization, d) assessment of the clinical significance of humoral immunity to these antigens in patients with cancer, and e) development of maximally immunogenic forms of cancer vaccines. Immunovirological studies will focus on selected human cancers that are suspected from serological, virological, and epidemiological evidence to be related to herpesviruses or papovaviruses. The following associations will be investigated: The relation of cytomegalovirus to Kaposi's sarcoma, genital cancer, and colon cancer; the relation of Epstein-Barr virus to nasopharyngeal cancer, and the relation of BK and JC papovaviruses to brain cancer, renal cancer, and cancers developing in immunodeficient patients. Using a variety of serological assays and reference viral antigens and antibodies to identify the range of herpesvirus and papovavirus antigens, evidence will be sought for the presence of viral antigens in human cancer cells and for the occurrence of corresponding antibody in patients with cancer as compared with the normal population.

281. RENAL CELL CARCINOMA WITH CHROMOSOMAL TRANSLOCATION

Schuman, S. M., University of Minnesota, Minneapolis Campus, School of Public Health, Dept. of Epidemiology, *1325 Mayo Memorial, Minneapolis, Minnesota*, 55455, United States of America

OBJECTIVES: Provide typing of currently recognized HLA-A,B,C, and DR locus antigens of these specimens upon request. HLA-A,B, and C typing will be performed on peripheral blood lymphocytes using a standard NIH microcytotoxicity technique. HLA-DR typing will be performed on B lymphocytes purified on nylon columns. Detection of the currently recognized A, B, C, and DR locus antigens will be done utilizing a standard typing tray. Results for each locus will consist of typewritten reports for each patient and will be reported to the Project Officer within three months of submission of each blood sample. Provide the Project Officer with a typewritten report of each patient's HLA typing that is labelled with the patient's name, identification number as given, and the date.

282. HUMAN RENAL CANCER AND HEMATOPOIESIS

Sytkowski, A. J., Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

We have derived a continuous line of human renal adenocarcinoma cells grown in vitro from a patient with renal cancer an erythrocytosis. The cells secrete into the growth medium an erythropoiesis stimulating factor which our results indicate is erythropoietin. We propose to clone this cell line and derive sublines with high erythropoietin secretory activity. These cells will permit us to isolate, purify to homogeneity and characterize substantial quantities of secretory erythropoietin and other secretory products and compare its (their) properties to those of human urinary erythropoietin by incubation of the cells with 3H, 14C, and/or 35S amino acids. These radioactive derivatives will serve as discrete probes of erythropoietin receptors on the red cell precursors of the marrow and will also make possible the development of a reliable and sensitive radioimmunoassay for the hormone.

283. IMMUNOCYTOCHEMICAL LOCALIZATION OF UROTHELIAL ANTIGENS IN NORMAL MOUSE BLADDER & CELL LINES DERIVED AFTER TREATMENT WITH CHEMICAL CARCINOGENS

Wilson, P., Trejdosiewicz, L. K., Imperial Cancer Research Fund, Cellular Pathology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Urothelial antigens were detected at the light and electron microscope levels using unfixed frozen and paraformaldehyde fixed sections and peroxidase-antiperoxidase - or indirect peroxidase - DAB techniques. The antiserum was raised in rabbits against calf bladder cytosol and absorbed against other epithelia (see Report 138). The antigen was localized in the urothelium of bladders from young adult and old mice and was also present in transformed cell lines derived from mouse bladder epithelium. At the electron microscope level, it was demonstrated that the majority of urothelial antigen was confined to the most differentiated superficial cell layer and was associated with structural cytoplasmic elements. In neoplastically transformed cells the localization was also cytoskeletal.

284. ESTABLISHMENT OF AN MRC SERUM AND BIOLOGICAL FLUIDS BANK FOR CANCER RESEARCH

Cooper, E. H., University of Leeds, Unit for Cancer Research, *Leeds LS2 9NL, England, United Kingdom*

OBJECTIVE: To collect and store specimens of serum and urine from patients with various types of cancer to provide material for evaluating biochemical tumor detection and monitoring systems.

APPROACH: The bank is mainly concerned with lymphoid malignancies and gastrointestinal and urological cancer.

PROGRESS: The bank is being used partially by the Unit for Cancer Research, and partially to supply other laboratories (e.g., evaluation of the immunological detection of prostatic acid phosphatase in conjunction with the Department of Medical Oncology, Charing Cross Hospital, London).

285. STUDIES ON THE IMMUNOLOGY OF GENITOURINARY TUMORS

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We continue to use immunological methods to study genitourinary (GU) tumors. We have developed several lymphoblastic cell lines which secrete interferon or interferon-like substances which significantly enhance the natural killer (NK) activity of normal lymphocytes when mixed with human tumor cells. We are characterizing and purifying these substances and intend to determine whether this product can inhibit the growth of urologic tumors in vitro and in nude mice with xenotransplanted urologic tumors. Such studies are an extension of our continued interest in NK cell activity which has been facilitated by our computerized image analysis system for studying cell mediated cytotoxicity. Additional efforts involve the cloning of human cytotoxic T-lymphocytes to renal cell carcinoma (RCC). In addition, we have begun the production of antibodies to these RCC antigens using hybridoma techniques. Finally, we

continue to investigate various tumor markers in testicular tumor. For example, we are evaluating the prognostic value of 'half-life decay curves' for alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG). We have determined that this analysis has unique clinical value and also have described the so-called 'release phenomenon' - paradoxical increases in serum marker levels at the initiation of therapy. Studies on SP-1 are continuing. Furthermore, we have evidence that placental alkaline phosphatase used in radioimmunoassays is a useful marker in seminoma. Finally, we are determining the micro-heterogeneity of molecular patterns of AFP using concanavalin-A chromatography. To date the patterns have been homogeneous although such analysis can be helpful in discriminating AFP of testicular tumor versus hepatic origin. Similar studies on the clinical utility of hCG molecular variation are underway.

286. SERODETECTION OF NEOANTIGENS IN UROGENITAL MALIGNANCIES

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Sequential serum samples from patients with urogenital malignancies (prostate, bladder, kidney) are analyzed immunoelectrophoretically vs. tumor extracts from the autochthonous host in order to determine those stages in tumor progression or regression at which tumor-directed antibody is detectable. Serum is tested under both non-dissociating conditions and conditions known to dissociate specific immune complexes. Relative immunoreactivity under normal and dissociating conditions provides a baseline to correlate clinical parameters in order to determine a prognostic index and to assess the impact of therapeutic modality. Those patient sera that show a high specific immune complex titer are chromatographically fractionated to enrich for the reactive antibody component of immune complexes.

Patient sera which exhibit a high titer vs. autochthonous tumor extract are further analyzed by two-dimensional SDS-polyacrylamide gel-immunoelectrophoresis; such two-dimensional analyses should provide a consistent molecular weight profile for those antigens in prostate, bladder, and kidney carcinomas that are recognized by humoral antibodies in patient sera.

287. DETECTION OF UROGENITAL NORMAL AND NEOPLASTIC ANTIGENS

Green, R. W., Paulson, D. F., Mickey, D. D., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina*, 27710, United States of America

A direct in vitro binding assay which is sensitive and quantitative for detection of specific antigens on the surface of cultured human urogenital tumor cells has been developed in our laboratory. The immunoglobulin (IgG) fractionated from rabbit antisera is radiolabeled with 125I to obtain sensitivity in measuring the antigens present on the test cells. Adsorption of IgG with normal non-urogenital tissue enables the detection of both organ specific antigens (OSA) and tumor associated antigens (TAA). Further adsorption with normal urogenital tissue allows the detection of TAA. This assay will be compared with two other sensitive and quantitative binding assays for detection of specific surface antigens. The most effective assay will be used to monitor the isolation of membrane associated OSA and TAA from human urogenital tumor tissues grown in athymic nude mice and from tissues obtained at surgery and autopsy. Purified antigens will be used for the preparation of specific antisera requiring minimal adsorption. The purified antigens will also be used to develop direct and blocking radioimmunoassays for detection of TAA and OSA in body fluids. Clinical testing will begin when quantitative adsorption experiments indicate that the adsorbed antibodies are specifically detecting OSA or TAA. Serum and urine from patients with different stages of urogenital malignant diseases will be tested for their ability to block the binding assay. The degree of blocking will indicate the amount of OSA and TAA in these body fluids. This information will be used to evaluate the binding assay as a method for early detection and monitoring of urogenital malignancies.

288. COMPUTED TOMOGRAPHY IN EVALUATION OF ENDOCRINE PANCREATIC TUMORS, PANCREATIC AND KIDNEY CARCINOMA (ABBREV)

Hemmingsson, A., University Hospital, Dept. of Diagnostic Radiology, *S75014 Uppsala 14, Sweden*

OBJECTIVE: Evaluation of CT, gray scale ultrasonography, scintigraphy and conventional roentgenologic methods will be made in diagnosis, follow-up and spread of endocrine pancreatic tumors, pancreatic carcinoma and kidney carcinoma. Image enhancement with frequency filtration in computed tomography will also be investigated.

APPROACH: Phantom and clinical examination of liver, pancreas and kidney tumors.

289. CYTOLOGICAL MONITORING OF WORKERS EXPOSED TO AROMATIC AMINES IN A SYNTHETIC DYES PLANT

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Biennial cytological screening, together with wet urinary sediment examination and the urological control (cystoscopy), has been conducted since 1970 to study the effect of occupation on urinary bladder cancer. The results are correlated with age, sex, smoking habits, length of exposure and exposure levels. The cases discovered in the early phase have a high survival rate.

290. AUTOMATED DETECTION OF UROTHELIAL TUMOR CELLS

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The objective of our research is the automation and standardization of the morphological diagnosis of urinary cell sediments. The research was started with a semi-automated investigation of urinary cell preparations stained with a fluorescent bicolor method (acriflavine-Feulgen-stilbene). These preparations were screened manually for cells which on visual inspection appeared to have a high DNA content. The fluorescence of these nuclei was subsequently measured. This procedure allowed an evaluation of the usefulness of cells with a high DNA content as a prescreening criterion and as a diagnostic feature. The results in about 100 urinary cell preparations showed that all grade II, III and IV tumors did contain cells with a high DNA content. These cells were rarely detected in some benign conditions such as inflammation and calculi, but never in normal urine from control persons. For automated screening a television based system is used. Programming and construction of the LEYTAS (Leyden Television Analysis System) image analysis computer were performed in co-operation with the Centre Morphologique et Mathematique, Fontainebleau, and Leitz, Germany. Preliminary results show a very effective separation between negative and positive preparations and detection with an extremely low number of artifacts of all positive preparations. Further research will be concentrated on implementing more advanced nucelar parameters programs (e.g., details of chromatin distribution within the nucleus) in LEYTAS. Also a larger field trial will be carried out.

291. QUANTITATIVE URINARY CYTOLOGY OF FOSSIL FUEL WORKERS

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The objective is to develop and apply quantitative methods for the cytological evaluation of uroepithelial cells exfoliated into the urine of workers in high-risk fossil fuel extraction, conversion, and utilization industries. Image analysis will measure the amount, localization, and spatial distribution of cytochemical probes and will be used to detect differences between normal and abnormal uroepithelial cells. Quantitative cytochemical probes will reflect cellular properties such as enzymatic activity, membrane structure, and chromatin condensation. Measurements will be correlated with conventional cytomorphologic identification to evaluate the diagnostic potential of the various probes. The project should result in the reliable and early detection of cancerous changes in the uroepithelium. For the individual, the lesion will be detected at an early, treatable

and perhaps reversible stage. For society, a hazardous situation will be identified so that early remedial action can be taken.

292. BIOLOGIC TUMOR MARKERS IN THE CELLS AND SERA OF PATIENTS WITH UROLOGIC CANCERS

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Techniques have been developed to localize and quantitate biologic tumor markers in the cells and sera of patients with urologic cancers. These markers include human chorionic gonadotropin, alpha-fetoprotein, pregnancy specific beta 1 glycoprotein (SP1), different isoenzymes of lactic dehydrogenase (LDH), ABO(H) antigens, and steroid receptors. These markers have been correlated with the histology, grade, stage, and management of patients with urologic cancers. Experimental animal models of cancer induction for the kidney, bladder, prostate, and testis have also been developed. These animal models are being utilized to study the role of cytoreductive surgery, chemotherapy, and immunotherapy of these urologic cancers. Athymic mice have been utilized for xenograft of testicular tumor that produces markers. By utilizing specific antibody labeled with a gamma-emitting radioisotope such as 131I, the role of radioimmunodetection and radioimmunotherapy is being investigated in testicular and prostatic cancer.

BIBLIOGRAPHIC REFERENCES: Javadpour, N., Woltering, E.A., and Soares, T.: Simultaneous measurement of tumor cytosol and peripheral serum levels of HCG and AFP. Invest. Urol., in press (June 1980). Javadpour, N.: Radioimmunoassay and immunoperoxidase of pregnancy specific beta 1 glycoprotein (SP1) in certain testicular cancer. J. Urol., in press (April 1980).

293. CYTOLOGIC CHARACTERIZATION OF RAT UROTHELIUM

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The goal of this project is to use the solid-state automated microscope (SSAM), developed under NIH grants GM 25107 and GM 27044, and other quantitative image analysis tools to characterize cells exfoliated from normal and malignant urothelium. Such characterization could then be used as the basis for a device for prescreening exfoliated cellular specimens for bladder cancer in high risk populations and for assessing the potential toxic effects of known and suspected chemical carcinogens upon workers in the chemical industry.

Using a rat model system, we will apply quantitative image analysis and a variety of cellular cytochemical stains in order to determine which combination gives the best distinct characterization of normal, atypical, and malignant cell populations. The SSAM system would play a key role in this research in that it would permit rapid acquisition of a large number of cell images scanned at high resolution. Specifically a 2.2 mm by 2.2 mm field-of-view can be scanned at 0.6 micron spatial resolution in less than 1.2 seconds. For a well-prepared slide this means that more than 1000 cells per second may be acquired for high-resolution analysis.

For all of the stains to be examined the description to be analyzed can include: 1. Nucleus - size, shape, texture (chromatin distribution), stain content. 2. Cytoplasm - size, texture, stain content. Cell enzymatic content and distribution.

These descriptions of cells should lead to an incisive quantitative characterization of morphology that correlates with cyto- and histo-pathology.

294. IMMUNE RESPONSE TO AUTOLOGOUS HUMAN TUMORS

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OBJECTIVE: The aim of the project is the search for occurrence of tumor-related cell-mediated autoreactivity in patients with osteosarcoma, lung cancer and kidney cancer, and with various types of soft tissue sarcomas; the generation of secondary cytotoxicity against autologous tumor biopsy cells; the functional characterization of tumor infiltrating lymphocytes; and the search for the clinical relevance of the in vitro obtained test-results.

APPROACHES: In an effort to eliminate at least some of the factors which hamper interpretation of in vitro results when tumor cell lines are used as the antigen source, two tests have been designed in our laboratory for measuring tumor-related autoreactivity in man, the autologous tumor stimulation (ATS), and autologous lymphocytotoxicity (ALC). In both assays, tumor cells separated from biopsy specimens are allowed to react with autologous lymphocytes. Cytotoxicity against tumor biopsy cells will be tested directly and also after cocultivation of lymphocytes with the autologous tumor biopsy cells.

PROGRESS: The most important finding was the detection of lymphocytes which could respond with proliferation and with generation of cytotoxic lymphocytes after an in vitro exposure to autologous tumor biopsy cells. The genuine tumor relatedness of this function was indicated both by the autologous restriction for reactivity in ATS and the secondary cytotoxicity generated in vitro with similar autologous reactivity. The in vivo relevance of the ATS was indicated by its correlation to the delayed type cutaneous hypersensitivity (DCH) reaction evoked by tumor extracts. The ATS reactive cells were found within the T-lymphocyte fraction.

295. IMMUNOLOGIC RESPONSE IN PATIENTS WITH KIDNEY CARCINOMA TO KIDNEY CARCINOMA EXTRACTS

Fossati, G., Canevari, S., Della Porta, G., Miotti, S., Pizzocaro, G., Valente, M., Cataldo, I., Grandi, C., Istituto Nazionale per lo Studio e la Cura dei Tumori, Division of Experimental Oncology A, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: To isolate and purify tumor-associated antigens obtained from fresh specimens of kidney carcinoma.

APPROACH: Crude soluble material of renal carcinoma and normal renal tissue, obtained by 3M KCl either directly from surgical specimens or from crude membrane preparations, will be further purified by gel-filtration, ultracentrifugal flotation in KBr and polyacrylamide gel electrophoresis. The immunogenicity and specificity of these preparations will be assessed by delayed cutaneous hypersensitivity reaction (DCHR) and by two in vitro tests: the leukocyte adherence inhibition test and the agarose leukocyte migration inhibition test.

296. SOLID TUMORS AND STEROID RECEPTORS

Conti, C., Concolino, G., Marocchi, A., Sciarra, F., Bracci, U., Di Silverio, F., Tenaglia, R., Picardi, C., Universita degli Studi di Roma, Istituto di Clinica Medica V, *Viale del Policlinico, 00100 Rome, Italy*

OBJECTIVE: Study of steroid receptors in breast cancer, prostatic carcinoma and renal cell carcinoma in order to evaluate the hormone dependence of the tumors and the response to endocrine treatment.

APPROACH: Dextran-coated charcoal method and agar gel electrophoresis to evaluate cytosol receptors in primary tumors.

PROGRESS: Follow-up of patients with receptor positive mammary tumors treated with TAM. Follow-up of prostatic cancer patients treated with orchiectomy and CPA. Follow-up of patients with hormone-dependent renal cell carcinoma, treated with nephrectomy plus MPA at pharmacological doses.

297. NEPHROPATHY ASSOCIATED WITH TUMOR

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In order to examine the role of circulating immune complexes in patients with renal cell carcinoma, a new method of quantitation of circulating immune complexes was developed using Sepharose 4B coated with antibody to human C3, which acted as C3 receptors. Serum samples were collected from 24 normal volunteers, 30 systemic lupus erythematosus (SLE) patients, 20 rheumatoid arthritis (RA) patients and 13 subacute bacterial endocarditis (SBE) patients. Circulating immune complexes levels were 2.0 plus or minus 1.7 micrograms/milliliter in normal volunteers, 48.9 plus or minus 65.5 micrograms/milliliter in SLE patients, 116 plus or minus 98.4 micrograms/milliliter in RA patients and 340.2 plus or minus 357.1 micrograms/milliliter in SBE patients. If the normal circulating immune complexes level was set with plus or minus 2S.D. of mean value of normal

volunteers, the positive results were found in 1/24 of normal volunteers, 19/30 of SLE patients, 19/20 of RA patients and 12/13 of SBE patients. This method appears to be simple, reproducible and sensitive. Using this new method, circulating immune complex level will be quantitated in the serum of patients with renal cell carcinoma and the constituents of the immune complexes will be analyzed.

298. IMMUNE RECOGNITION OF AUTOLOGOUS RENAL CELL CARCINOMA

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Tumor antigens have been identified in renal cell carcinoma, in the tumor membrane lymphocyte stimulation assay and with autologous antibodies. Stimulation of autologous lymphocytes with tumor plasma membranes provides a unique approach for determining the responding lymphocyte population in vitro and a determination of the responding cells immunological function. A positive in vitro blastogenic response was observed in 1/3 of the patients in these studies. Our studies in vitro demonstrate that the responding lymphocytes are primarily T-suppressor cells. Future studies will be directed towards establishing a correlation between the immune response, the responding populations, and the clinical course of the patient. The importance of the genetic restriction of this response and the clinical course of the patient remains to be determined.

BIBLIOGRAPHIC REFERENCES: Hemstreet, III, G.P., Enoch, P.G., Pretlow, II, T.G.: Tissue disaggregation of human renal cell carcinoma with further isopyknic and isokinetic gradient purification. Cancer Res 40:1043-49, 1980. Troner, M.G. and Hemstreet, III, G.P.: Cyclophosphamide, Adriamycin, and Cis-Dichloro-diammineplatinum (II) (CAP) in the treatment of Urothelial Malignancy: A Pilot Study of the Southeastern Cancer Study Group. Cancer Treatment Reports (In Press), 1980.

299. CELL-SURFACE ANTIGENS OF RENAL CANCER, ASTROCYTOMA, LEUKEMIA AND LYMPHOMA

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This is part of a broader project. A summary of this subproject is not available.

2. CHEMOTHERAPY

300. NEPHROBLASTOMA - ADJUVANT CHEMOTHERAPY

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A therapeutic protocol for nephroblastoma is now in progress and a national study is being organized.

301. ADRIAMYCIN CARDIO- AND NEPHROTOXICITY (ABBREV)

Bizzi, A., Donati, M. B., Poggi, A., Veneroni, E., Codegoni, A. M., Delaini, F., Semeraro, N., Villa, S., Istituto di Ricerche Farmacologiche Mario Negri, Lab. of Lipid Metabolism/Hemostasis & Thrombosis, *Via Eritrea 62, 20157 Milan, Italy*

The aim of this project is to investigate in rats biochemical mechanisms responsible for cardio- and nephrotoxicity induced by adriamycin and other analog antibiotics interfering with DNA.

Phospholipid fatty acid metabolism and lipid peroxidation will be investigated and related to the injury of tissues.

Hyperlipemia and hypercoagulability observed in adriamycin treated rats will be studied in regard to their onset and as they relate to cardio- and nephrotoxicity. Results obtained describe the nephrotic syndrome of rats as a 'minimal change' glomerulonephritis, with a significant polianion loss detectable as early as 3 hr after injection. Hypercoagulability and hyperlipemia appeared about 2 weeks after injection. Hypercoagulability was found to be due to increased fibrinogen and factor VIII level, short activated partial thromboplastin time, low antithrombin levels and depressed fibrinolytic activity.

Increased tendency to arterial thrombosis was observed. Hyperlipemia characterized by alteration of VLDL, LDL and HDL, might be partially due to decreased lipoproteinlipase activity or content of adipose tissue. Kidney phospholipids were depressed.

302. AUGMENTATION OF ALKYLATING AGENTS WITH DMSO

Aisner, J., Wiernik, P. H., Ostrow, S., Egorin, M., Bachur, N., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Medical Oncology, *Baltimore, Maryland,* 21201, United States of America

A number of advanced cancers such as renal cell carcinoma and squamous cell carcinoma of the lung have proven particularly refractory to chemotherapy. It is therefore warranted to test new agents or new experimental modalities in these tumors. Animal studies suggest that the chemotherapeutic activity of certain alkylating agents can be augmented by the use of dimethylsulfoxide (DMSO). Patients with metastatic squamous cell carcinoma were therefore tested with DMSO and cyclophosphamide. Ten patients with squamous cell lung cancer have been started on DMSO plus cyclophosphamide. There have been no objective anti-tumor responses seen in three patients, but it is too early to determine overall activity of this combination. Pharmacokinetics have been initiated to determine if the DMSO changes the disposition of the cyclophosphamide. So far no differences have been noted where each patient serves as his/her own control.

BIBLIOGRAPHIC REFERENCES: Aisner J., Wiernik P.H.: Thio-TEPA (NSC-6396) and dimethylsulfoxide (NSC-763) in the treatment of renal cell carcinoma. Cancer Clinical Trials 1:20-25, 1978.

303. INITIAL DRUG THERAPY FOR METASTATIC RENAL CELL CARCINOMA

Van Echo, D. A., Wiernik, P. H., Aisner, J., Fuks, J., Markus, S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Oncology Section, *Baltimore, Maryland,* 21201, United States of America

AMSA has been given to 16 patients with renal cell carcinoma (RCC) without therapeutic effect and this study is closed. Chemotherapy failures are then given medroprogesterone and tamoxifen. To date, 0/10 patients have responded but this study is still in its preliminary stages and is being continued.

BIBLIOGRAPHIC REFERENCES: Van Echo, D.A., Markus, S., Aisner, J., Wiernik, P.H.: A Phase II trial of AMSA in patients with metastatic renal cell carcinoma. Cancer Treatment Reports (in press), 1980.

304. CALGB NO. 7971 - PHASE II STUDY OF M-AMSA - TREATMENT FOR MELANOMA, OVARIAN CARCINOMA, BREAST CARCINOMA, HYPERNEPHROMA AND HEPATOMA

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M-AMSA (NSC No. 259992) is a synthetic anti-tumor agent which inhibits DNA synthesis by intercalation and external binding to DNA. Phase I studies have suggested activity against melanoma, ovarian carcinoma, breast carcinoma, hypernephroma, hepatoma, and certain sarcomas.

PURPOSE: A Phase II study to determine the efficacy of this agent in melanoma, ovarian carcinoma, breast carcinoma, hypernephroma, and hepatoma; and to determine the safety of this agent in clinical use.

PLAN: Patients with advanced tumors of above types, unresponsive to usual therapeutic agents, receive M-AMSA 120 mg/m2 IV at 3 week intervals, with dose escalation of 20 mg/m2 q 3 week until myelosuppression develops or maximum dose of 160 mg/m2 is reached. Dose is modified for myelosuppression or hepatic dysfunction. Therapy continues until relapse, or through 2 complete courses at maximum dose if no response occurs. Information on tumor response and drug toxicity is submitted to CALGB for analysis as a part of their multi-institutional study.

305. PHASE II STUDY OF VINDESINE

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OBJECTIVES: This project is designed to test the new anti-neoplastic agent Vindesine in the treatment of patients with various malignancies to determine the effect of this drug in patients with otherwise untreatable lung cancer.

PLAN: Patients with various types of carcinoma, including patients with renal cell carcinoma, bronchogenic carcinoma and other types of malignancies, who have failed standard therapy will be treated with a new agent, Vindesine. This drug has been found to be active in animal tumors.

METHODS: Vindesine will be supplied by Eli Lilly Company. Patients who have no other treatment options available to them will sign an informed consent before entry under the study. All patients will be required to have measureable disease. Patients will be treated with Vindesine given as a dose of 3 mg/m2 weekly and the toxicity of this drug as well as evidence of tumor shrinkage will be closely monitored.

CLINICAL RELATIONSHIP: It is hoped that this study will be able to demonstrate a drug which will be effective in the treatment of cancer.

306. PHASE II STUDY OF ANGUIDINE IN SOLID TUMORS

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Anguidine is a Phase II investigational drug that is being evaluated for the use in patients with solid tumors who have been shown to be refractory to standard therapy. This investigational drug has been shown in the mouse model to be effective against the P388 leukemia model and the murine colon tumor. The side effects have not been excessive in animal and in man, however, every effort will be made to monitor closely any side effects that may occur. It will be tried against the following tumors: Hodgkin's disease refractory to treatment, non-Hodgkin's lymphoma, breast cancer, oat-cell carcinoma of the lung, adenocarcinoma, large cell and epidermal carcinoma of the lung, GI cancers such as cancers of the stomach and the pancreas, sarcomas, ovarian carcinoma, endometrial carcinoma, renal cell carcinoma and testicular carcinoma. It is hoped that by studying this agent we will demonstrate an effectiveness in one of these human tumors and therefore add a good anti-cancer drug to our present chemotherapeutic regimen.

307. PHASE II STUDY OF MAYTANSINE IN SOLID TUMORS

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee,* 38104, United States of America

This is a Phase II study of the investigational drug, Maytansine, against human solid tumors that have been previously refractory to standard therapy. This drug has demonstrated good activity against the mouse P388, a lymphocytic leukemia model. The side effects are not excessive, at least in early human and animal models. Several human tumors, including oat cell carcinoma of the lung, malignant melanoma, and cancers of the breast and head/neck demonstrated in Phase I studies some response rates. We will test this drug in patients who have been refractory to Hodgkin's disease, non-Hodgkin's lymphoma, breast, small cell of the lung and non-oat cell carcinoma of the lung, GI tract carcinoma, sarcomas, ovarian carcinoma, endometrial carcinoma, renal carcinoma and testicular carcinoma. It is hoped that by testing this drug we will add a new drug to our chemotherapeutic regimen for this group of diseases in which therapy is inadequate.

308. SWOG 7860, EVALUATION OF MGBG IN SOLID TUMORS AND REFRACTORY HEMATOLOGIC MALIGNANCIES

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SWOG 7860 - The objectives of this study are to determine response rate and remission duration with primary weekly intravenous therapy using MBGB in patients with advanced esophageal, breast, pancreatic, colorectal, and head and neck carcinomas and lymphoma; and to define the qualitative and quantitative toxicity of this regimen.

MBGB is intended as initial chemotherapy for patients with inoperable or disseminated renal, esophageal, and pancreatic carcinoma. It is intended for use in patients with other forms of advanced malignancy (breast, head and neck, colorectal, lymphoma and multiple myeloma) if their disease has become progressive after initial chemotherapy and they are not candidates for SWOG studies of higher priority. The dose of MBFB is 500 mg/m2 to be given as an intravenous infusion in D5W or normal saline over no less than 30 minutes, into a freely running IV weekly. One hundred and nine patients with advanced malignancy, refractory to conventional therapy, were treated with a weekly schedule of methyl-GAG. Ninety-one patients (83%) were less than fully ambulatory. Sixty-five patients were fully evaluable for response. There were two complete and nine partial responses. An additional nine patients had objective tumor regressions and were classified as improved. The median duration of response was 5 months. Toxic effects were primarily mucositis (17 patients) and nausea and vomiting (14 patients). Sixty-seven patients had no manifestations of drug toxicity. Responses observed in a wide variety of solid tumors warrant further clinical trials.

309. CIS-DIAMINEDICHLORO PLATINUM IN CANCER PATIENT WITH RENAL IMPAIRMENT

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This is part of a broader project. A summary of this subproject is not available.

310. HORMONAL THERAPY OF ADVANCED RENAL CELL CARCINOMAS

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In this study of patients with advanced measurable renal cell carcinoma, we are assessing combined hormonal therapy - high dose androgen with provera. Whenever possible, receptor study of tumor tissue is being carried out. In the past year four cases have been added to this trial. The study is continuing.

311. EVALUATION OF ANTI-ESTROGEN, TAMOXIFEN, AND ESTROGEN IN ADVANCED RENAL CELL CARCINOMA REFRACTORY TO ANDROGEN AND PROGESTERONE

Papac, R. J., Eisenfeld, A., Weininger, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *W. Spring St., West Haven, Connecticut,* 06516, United States of America

This study is designed to determine whether renal cell carcinoma refractory to combination hormonal therapy will show response to tamoxifen. It is established that renal cell carcinoma cells often have receptors for estrogen and progesterone. Since the binding affinity seems weak, it is postulated that large doses of hormones may be necessary to elicit antitumor effects with hormonal treatment. This rationale may also apply to the use of the anti-estrogen, tamoxifen. For this reason, in this investigation, we are applying high doses of tamoxifen, and attempting to correlate responsiveness to the presence or absence of tissue receptors for the hormones, when possible.

The study now includes 5 patients; the major effect appears to be disease stabilization. The study is continuing.

312. REDUCTION OF TOXICITY IN CANCER CHEMOTHERAPY

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Nephrotoxicity in patients on long-term platinum (II) chemotherapy constitutes a limit both in dosage and duration of chemotherapy; successful use of adjuvant platinum chemotherapy requires a solution to this problem. The principal investigator has recently demonstrated the success of a dithiocarbamate rescue procedure to inhibit nephrotoxicity in an animal model. The research proposed herein is designed: (1) to provide information about the interaction of dithiocarbamate with membrane-bound platinum and platinum DNA complexes and hence increase our knowledge of the mechanism of platinum toxicity; (2) to confirm that cis-platinum, when given in combination with dithiocarbamate, is still effective as an anti-tumor agent; (3) to

demonstrate that oral disulfiram is an effective rescue agent for platinum toxicity. The interaction of dithiocarbamate and preformed complexes of platinum with renal tubular membranes and with DNA will be evaluated spectrophotometrically to determine whether dithiocarbamate can remove platinum from these complexes. Administration of cis-platinum and dithiocarbamate will be carried out in tumor-bearing animals and the effect of the drug combination on tumor size compared with that of platinum alone. The pharmacokinetics of oral disulfiram in the rabbit will be explored as a model for this drug as a rescue agent in a clinical setting.

BIBLIOGRAPHIC REFERENCES: R.F. Borch, J.H. Markovitz, and M.E. Pleasants, A New Method for the HPLC Analysis of Pt(II) in Urine, Anal. Lett., 12 (B8), 917-926 (1979). R.F. Borch and M.E. Pleasants, Inhibition of cis-Platinum Nephrotoxicity by Diethyldithiocarbamate Rescue in a Rat Model, Proc. Nat. Acad. Sci. (USA) 76 (12) (December 1979).

313. SUPERDOSIS CANCER CHEMOTHERAPY OF HUMAN TUMORS GROWN IN NUDE MICE WITH DIMETHYL MYLERAN AND AUTOLOGOUS BONE MARROW INFUSION

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OBJECTIVES: To test the sensitivity of human tumors grown in nude mice to superdosis chemotherapy with dimethyl Myleran followed by bone marrow transplantation.

APPROACH: Human tumors, including melanomas, hypernephromas, bronchial carcinomas and colon carcinomas, are serially maintained in nude mice. Panels of nude mice carrying these tumors are subjected to lethal doses of dimethyl Myleran (DMM) followed by isogeneic bone marrow. Tumor response and survival are followed. In particular, we are now interested in determining whether individual tumors of the same type display a heterogeneic or a similar sensitivity to this chemotherapeutic protocol. If the latter is the case, the intended therapeutic scheme could be applied clinically without testing the sensitivity of every single tumor to DMM beforehand. Moreover, it is planned to study whether the lethality of tumor-eradicating doses of DMM can be overcome also by autologous bone marrow transplantation.

PROGRESS: Several but not all of the tested tumors can be completely eradicated with the above scheme. The effect of supplementary submarginal T-cell doses was also studied. A preliminary report has been published.

BIBLIOGRAPHIC REFERENCES: Zurich Ed. W. Siegenthaler and P. Luthy. Americ. Soc. for Microbiol., Current Chemotherapy 2, 1146-1148, 1978.

314. RENAL TOXICITY OF CIS-PLATINUM - MECHANISM, PATHOPHYSIOLOGY, PROTECTION

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No summary has been provided to the Smithsonian Science Information Exchange.

315. CLINICAL EFFECTS OF ADRENAL STEROIDS ON RENAL FUNCTION IN CANCER PATIENTS

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This is part of a broader project. A summary of this subproject is not available.

316. PROTOCOL 9 - PHASE II, MASTER PROTOCOL EVALUATION OF NEW AGENTS FOR THE TREATMENT OF PATIENTS WITH ADVANCED UROTHELIAL CANCER

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This Protocol outlines the procedures designed to screen new chemotherapeutic agents for activity in patients having advanced urothelial carcinoma resistant to, or progressing on, treatment with standard agents. A fixed sample-size study design will be used, with a stopping rule to avoid continued use of a drug that appears unlikely to meet minimal anti-tumor activity criteria. The patients registered to this Protocol will have histologically confirmed urothelial carcinoma with manifestations of regionally advanced or metastatic cancer or with residual bladder tumor with muscle invasion. Bladder cancer in these patients must be beyond hope of surgical or radiotherapy cure. These patients will have been treated and progressed on protocols of higher priority (Protocols 5 and 7) or not be eligible for treatment on these protocols. They will have failed chemotherapy with proven efficacy in bladder cancer or be deemed unsuitable candidates for such drugs. The patients will have measurable or evaluable disease.

The need for definition of drugs with activity in urothelial cancer and the indication of antineoplastic activity of mAMSA in early trials indicates that this drug be studied in a NBCCGA Phase II Protocol as the first agent.

Twenty-five patients with measurable disease are to be treated with each drug being tested.

317. EVALUATION OF NEW AGENTS FOR THE TREATMENT OF PATIENTS WITH ADVANCED UROTHELIAL CANCER

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Protocol 9 of the National Bladder Cancer Collaborative Group A is designed to screen new chemotherapeutic agents for activity in patients having advanced urothelial carcinoma resistant to, or progressing on, treatment with standard agents. Patients will have histologically confirmed bladder carcinoma (regionally advanced, metastatic, or residual tumor with deep muscle invasion). Bladder cancer in these patients must be beyond hope of surgical or radiotherapy cure. Patients should have been treated and progressed on protocols 5 or 7, or not be eligible for these protocols. Patients should have failed chemotherapy with proven efficacy in bladder cancer.

m-Amsa will be given at 90mg/m2 every three weeks. All patients receive two courses of therapy. The first interim evaluation is made 6 weeks after initiation of therapy, prior to administration of the 3rd course. Patients with progressive disease will be taken off therapy. All other patients continue on therapy until disease progression or unmanageable toxicity occurs. All patients are followed until death.

318. CHEMOTHERAPY OF ADVANCED UROTHELIAL CANCER

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A collaboration of four institutions will evaluate the clinical effectiveness of antineoplastic chemotherapy in patients with evaluable objective parameters of advanced urothelial cancer utilizing a common protocol, standard report forms, and a common statistical center. Patients will be randomized between two chemotherapy arms: one arm, adriamycin, common to the collaborating institutions, and the other arm generated within each collaborating institution, cyclophosphamide plus diamine dichloride platinum at MSKCC. The common treatment arm will provide the standard against which the results of the different intra-institutional treatment regimens may be judged. Identification of a superior treatment by a participating institution will justify its adoption as the new inter-institutional standard against which the search for still better regimens will continue. The program will parenthetically provide an opportunity to assess the validity of various parameters of tumor response against standard criteria and to assess the reproducibility of results of a common treatment within different institutions.

319. THE CHEMOTHERAPY OF METASTATIC GENITOURINARY TUMORS

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Cis-platinum and adrimycin have been shown to have activity against testicular carcinoma. This drug combination was used for genitourinary neoplasms. Thirty-nine patients received therapy with platinum and adriamycin. Complete responses occurred in five of 11 patients. Partial responses occurred in four

patients with testicular carcinoma. The median duration of response will exceed eight months. Partial responses have been seen in one patient with Wilms' tumor, 5/9 patients with bladder cancer, 4/9 patients with ovarian cancer and 1/4 patients with prostate cancer. Two patients are too early to evaluate, and three patients were evaluable only for toxicity. Dose reduction and delay in therapy was necessary because of bone marrow suppression. Nephrotoxicity occurred in 7 patients and necessitated discontinuing platinum one. Other toxicities included ototoxicity and neurotoxicity. The combination of platinum and adriamycin is active against advanced genitourinary neoplasms and further studies are comtemplated to enhance therapeutic efficacy. Other combinations will be used for testicular cancer.

320. CORRELATED STUDY OF METABOLIC REGULATION IN NEOPLASIA

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The purpose of the present proposal is to strengthen and expand the research programs in metabolic regulation and neoplasia in the Laboratory for Experimental Oncology.

The individual research projects include investigations of (1) regulation of metabolism and cellular proliferation in mammalian cells, (2) enzyme pattern-directed experimental chemotherapy of hepatomas and renal cell carcinomas, (3) regulation of purine degradation and salvage pathways, (4) regulation of key enzymes of IMP biosynthesis and degradation in normal and neoplastic cells, (5) control of thymidine metabolism, (6) somatic cell hybridization in elucidation of the role of metabolic imbalance in neoplastic transformation and progression, and (7) karyotype and chromosome banding pattern and enzymology in hepatomas and in somatic cell hybrids.

These investigations are directed to elucidate the control of gene expression as manifested in the altered metabolic regulation in neoplasia.

321. HORMONAL REGULATION OF KIDNEY EPITHELIAL CELL GROWTH

Taub, M. L., Hiller, S., Livingston, D., State University of New York, Health Science Center at Buffalo, School of Medicine, Dept. of Biochemistry, *3435 Main St., Buffalo, New York,* 14214, United States of America

The proposed research will evaluate the mechanisms by which hormones regulate the growth of kidney epithelial cells, and the alterations which occur upon malignant transformation. The MDCK cell line is particuarly advantageous as compared with other renal cell lines, for studies concerning hormonal regulation of growth as Medium K-1, a hormone supplemented, serum-free medium, has been developed which permits MDCK cells to grow in the absence of fetal calf serum. Following the methodologies developed in the laboratory of Dr. Gordon Sato, five supplements were identified (insulin, transferrin, T3, hydrocortisone and PGE1) which permitted MDCK cells to grow over a long term, and at an equivalent rate in serum-free and serum-supplemented medium. Medium K-1 has also been used to grow primary cultures of baby mouse kidney epithelial cells. Medium K-1 will be used for the following studies: (1) The possibility that PGE1 stimulates growth by increasing intracellular cAMP in MDCK cells will be examined. Available PGE1 independent variants of MDCK cells (variants which lack PGE1 requirement for long term growth in serum-free medium) will be utilized. 2) The possibility that malignant transformation is accompanied by changes in requirements of hormones for growth will be evaluated, utilizing available tumorigenic transformants of MDCK cells. (3) Growth regulation by hormones will also be examined in primary cultures of kidney epithelial cells. Medium K-1 was utilized to select epithelial cells from primary kidney cultures, whose growth responses to hormones resemble those of MDCK cells. In order to selectively grow different types of epithelial cells in primary kidney cultures, additional hormone-supplemented, serum-free media will be developed for kidney epithelial cell line which do not grow in Medium K-1.

322. CHEMOTHERAPY MODEL FOR RENAL CANCER

Williams, R. D., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Urology Section, *4150 Clement St., San Francisco, California,* 94121, United States of America

PROJECT OBJECTIVES: 1) To develop a chemotherapy model for human renal cell cancer using established human renal cancer cell lines and cultures of primary human renal cancer cells and 2) to establish in vitro parameters of cell response to chemotherapeutic agents that will correlate with in vivo responses and ultimately lead to development of effective treatment for patients with metastatic renal cell cancer.

PLAN: The response of renal cancer cells to treatment by a variety of chemotherapeutic agents will be tested in monolayer culture, a colony formation assay in agar, and on tumors produced in immune-deficient animals.

METHOD: Initially release of 125IUDR and polyamines into culture medium and levels in animal serum and urine will be studied as response variables.

CLINICAL RELATIONSHIP: Because at present there is no therapeutic agent or combination of agents known to produce objective responses in more than 25% of patients with metastatic renal cell cancer, a model to study potential agents with a capability of determining an efficacious regimen for treating each patient has highly relevant clinical importance.

323. TISSUE CULTURE OF MAMMALIAN UROTHELIUM

Paulson, D. F., Day, J. W., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina,* 27710, United States of America

Methodology has been developed for the rapid in vitro assay of chemotherapeutic drug effectiveness in human transitional cell malignancy (TCM). Drug killing of tumor cells is determined by percent inhibition in cell uptake of radioactive precursors of DNA, RNA, and protein. The assay requires only small amounts of tissue and is completed within seven days.

To assess the predictive value of this in vitro assay for the in vivo effectiveness of chemotherapeutic agents, responses of human tumors growing in athymic nude mice are being determined. Mice bearing human TCM are being treated with antitumor drugs and the effects estimated by change in tumor size. In vitro drug profiles are being determined for tumors removed from control mice receiving no drugs. In addition, in vitro drug profiles will continue to be constructed for surgical specimens.

The in vitro drug profiles will be compared to in vivo profiles from nude mouse supported tumors and to clinical data on patients undergoing chemotherapy. If the two drug profiles are similar, the in vitro assay would enable in advance of therapy the selection of the most effective drugs for each individual patient.

BIBLIOGRAPHIC REFERENCES: Wunderli, H., Mickey, D.D., and Paulson, D.F. C-Type Virus Particles in Human Urogenital Tumors After Heterotransplantation into Nude Mice. Br. J. Cancer 39:35, 1979.

3. IMMUNOTHERAPY

324. PRODUCTION OF TUMOR-SPECIFIC ANTIBODIES AGAINST MEMBRANE COMPONENTS OF HUMAN KIDNEY CARCINOMA

Birkmayer, G. D., Wieland, W., Schmidt, E., Ludwig Maximilians Universitat Munchen, Dept. of Cell Biology, *Goethestr. 33, D8000 Munich 22, Bayern, Federal Republic of Germany*

OBJECTIVE: Preparation of a specific antibody against tumor-specific surface components from human kidney carcinoma by immunizing sheep which have been made tolerant to normal kidney antigens in their embryonic phase.

APPROACH: Embryonic sheep are immunized against a membrane extract from normal human kidneys in order to make them tolerant. About 6 weeks after birth the young sheep are injected with identical extracts from human kidney carcinoma from the same patient from which the normal tissue was taken. The serum is tested after each booster injection and the one with the highest titer will be selected for further purification of the antibody.

PROGRESS: Pilot studies demonstrated that sheep still produce antibodies against normal kidney components even though they are immunized in their embryonic life span. However, antibodies against the tumor components have a higher

titre in the serum of the sheep preimmunized in their embryonic phase.

325. IMMUNIZATION WITH BCG AND ALLOGENEIC RENAL CANCER CELLS

Oettgen, H. F., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

OBJECTIVES: Determine whether the cells of renal cancers have cross-reacting tumor-associated antigens by performing tests for humoral immunity to autologous tumor cells before and after immunization with BCG and allogeneic renal cancer cells. Attempt to analyze the specificity of the serological reactions and to investigate the patterns of antigen expression in terms of culture time, growth characteristics, and cell cycle kinetics. Periodic assessment of humoral immunity will be performed on sera from patients with Stage I renal cancer receiving conventional therapy and on sera from patients with Stage II, III, and IV renal cancer who are immunized with BCG and allogeneic renal cancer cells. It is expected that twenty patients per year will be entered on the study. Any modification of the laboratory or clinical studies must have the prior approval of the Project Officer before being instituted.

326. POLYMERIZED TUMOR ANTIGEN-ADJUVANT IMMUNOTHERAPY

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The presence of tumor-directed immune responses and absence of alternative modes of therapy make renal carcinoma an excellent model for immunotherapy in humans. Preliminary data from two institutions suggest that polymerized tumor antigens admixed with an adjuvant (PTA/Ad) can induce tumor regression and possibly increase survival in patients with disseminated renal carcinoma.

We propose a randomized prospective trial of PTA/Ad versus standard hormonal therapy in patients with measurable metastic lesions and a randomized double-blind trial of PTA/Ad versus adjuvant plus placebo in patients without clinical disease but with a high risk of recurrence. Frequency of treatments, dose of antigen, and the adjuvant will be changed to achieve evidence of general and tumor directed cellular immune reactivity as measured by serial skin tests and in vitro testing. Results of in vitro testing and skin tests will be correlated with disease status and clinical response by multivariate analysis. Statistical evaluation of clinical response, disease-free intervals, and duration of disease stability should allow determination of the efficacy of PTA/Ad immunotherapy in a human tumor model.

327. IMMUNOTHERAPY OF CANCER WITH IMMUNE RNA

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PROJECT OBJECTIVES: This research project was designed to see if there is a therapeutic benefit derived from the administration of xenogeneic immune RNA to patients at high risk of developing recurrence following curative resection for renal cell carcinoma. Patients admitted to this study had positive nodes at the time of nephrectomy, or have had capsullary invasion of the kidney by tumor.

RESEARCH PLANS: Xenogeneic immune RNA is extracted from sheep immunized with human renal cell carcinomas. Following nephrectomy, those patients are randomized to receive weekly intradermal RNA injections or to be included in a control group. Those receiving therapy receive treatment for one year. Survival and time to recurrence are being compared for each group.

METHODOLOGY: Patients receive skin testing to DNCB and common dermal antigens and have serum and lymphoid cells obtained and freeze-preserved at three-month intervals. Immune assays such as complement fixation to measure anti-renal cell cancer antibody and lymphocyte mediated cytolysis of renal cell cancers are being performed. An effort is being made to see if there are any changes in these donors which suggest protein synthesis or formation of antibody to a sheep idiotype. Immunization of sheep, RNA extraction, purification and storage of immune RNA, randomization, patient monitoring, and immunologic testing are all part of this study.

CLINICAL RELATIONSHIP: This adjuvant therapy study has a direct clinical relationship to the management of patients with renal cell malignancies. Adjuvant therapy is particularly attractive to this group of patients since virtually no effective systemic therapy exists for recurrent metastatic disease.

FINDINGS: There has been absolutely no demonstrable toxicity associated with treatment. Among the 12 patients who have received adjuvant immune RNA, there have been no recurrences. Follow-up will be required to see if this treatment is effective.

328. ADOPTIVE IMMUNOTHERAPY IN RENAL CELL CARCINOMA PATIENTS

Mannick, J. A., Richie, J. P., Steele, G., Wang, B. S., Zellen, M., Frei, E., Ervin, T., Wilson, R. E., Harvard University, Boston Campus, Peter Bent Brigham Hospital, Dept. of Surgery, *721 Huntington Ave., Boston, Massachusetts*, 02115, United States of America

No reliable means of therapy exists to date for patients with advanced renal cell carcinoma (RCC). This proposal concerns the application of the transfer of cellular immunity by immune RNA (I-RNA) in a randomized clinical trial in patients with renal cell carcinoma. Prior animal studies performed in our laboratory, utilizing a syngeneic mouse tumor host system, have indicated that immunotherapy with syngeneic spleen cells incubated in vitro with specific I-RNA raised in guinea pigs prevented death from pulmonary metastases in mice after excision of the primary tumor. In addition, Phase I studies of patients with metastatic RCC using the treatment plan detailed in this proposal have been completed. Preliminary results have demonstrated the following: 1) The I-RNA treated syngeneic lymphocyte infusions are well tolerated; 2) in vitro parameters of host anti-tumor response do reflect increased specific cell mediated cytotoxicity (CMC) against tissue-type specific tumor associated antigens after in vivo treatment; 3) there is no evidence of tumor growth acceleration after treatment; 4) objective response of tumor regression has been observed in some patients after treatment. The proposed clinical study will be modeled on our experimental systems. Patients with Stage II RCC with extension into the inferior vena cava, Stage III RCC with positive regional lymph nodes, or Stage IV tumor with measurable disease in a prospective randomized trial will receive immune RNA therapy or standard therapy beginning approximately three weeks after excision of the primary tumor. I-RNA will be extracted from the lymphoid tissues of guinea pigs immunized against the patient's own tumor and will be incubated in vitro with the patient's peripheral blood lymphocytes. These autologus lymphocytes will then be returned to the patient intravenously after incubation. Correlation between in vitro parameters of tumor specific immunity and the patient's tumor-free survival will be sought utilizing tests for tumor specific CMC, complement dependent cytotoxicity, antibody dependent CMC and natural killer cell activity.

329. BCG IMMUNOTHERAPY OF RENAL CELL CARCINOMA

Lamm, D. L., Radwin, H. M., Banowsky, L. H., Shain, S. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Urology Section, *San Antonio, Texas*, 78284, United States of America

The object of this proposal is to evaluate in a phase II historically controlled clinical trial the efficacy of regional BCG immunotherapy in patients with locally extensive or metastic renal cell carcinoma. Response rates based on the generally excepted criteria for complete (no evidence of disease) and partial (greater than 50%) reduction of measurable disease. Objective remissions as well as survival comparisons will be made with historical controls. To date 11 patients have enrolled in the study. One patient has expired of metastatic renal cell carcinoma. This patient who had extensive liver metastasis at the time of presentation survived 5 months after treatment. The median reported survival for such patients is three months. Although several other patients with metastatic disease have had subjective responses with improvement of performance status, no objective responses have been seen. One complication of immunotherapy, a retroperitoneal flank BCG abscess, which required

incisional drainage and isoniazide therapy occurred. This patient did not return for his post-operative clinic visit and therefore did not receive isoniazide as directed by the protocol. None of the other patients who receive isoniazide have developed abcesses and medication is now prescribed at the time of discharge. It appears that BCG immunotherapy in renal cell carcinoma has an acceptable complication rate. Insufficient data is available at this time to access its efficacy. It is estimated that a total of 19 patients with metastatic disease will have to be studied to determine, with a rejection error of 5%, that this treatment has a level of therapeutic effectiveness of 15% or greater.

330. STUDY OF BACTERIAL COMPONENT IMMUNOTHERAPY IN CANCER

Vostka, G. J., Goldman, A., Gray, G., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The objectives of this research proposal are to determine, through clinical and laboratory studies, the toxicity, immunological effects, efficacy, mechanism of action and clinical role of chemically defined bacterial component immunotherapy in human malignant disease.

These objectives will be approached by detailed clinical Phase I, II and III studies of purified components used as single agents. The particular agents included in this current study are: aqueous suspension of M. smegmatis CWS; M. smegmatis CWS plus trehalose mycolate (P3) attracted to oil; and the Re glycolipid of Salmonella typhimurium. Phase I and II clinical studies of intravenous CWS and Re glycolipid will be done. Phase I studies will be done in patients with advanced lung cancer, sarcoma, melanoma and hypernephroma. Phase II studies will be done mainly in patients with malignant melanoma and hypernephroma. We have observed response in these patients and consider these diseases 'indicator systems' of active immunotherapeutic agents.

Concurrently, immune testing will be performed to define the immunological effects of these agents, and to attempt to identify patients who have a high probability of responding to these agents.

331. EXTRACORPOREAL IMMUNOABSORBENTS FOR IMMUNOTHERAPY OF NEOPLASTIC DISEASE

Terman, D. S., Baylor College of Medicine, School of Medicine, Dept. of Clinical Immunology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

This project is designed to continue the assessment of the efficacy of extracorporeal immunoadsorption therapy in treatment of various models of rheumatic and neoplastic diseases in the dog which have now produced promising results. We have developed several immunoadsorbents to which immune reactants have been chemically conjugated or physically entrapped. Each of these immunoadsorbents has been tested extensively in vivo in an extracorporeal circulation system in normal dogs and now in canine hosts with naturally occurring models of human disease, namely systemic lupus erythematosus and adenocarcinoma of the breast. Canine glomerular basement membrane antigen (GBM) has been physically entrapped in a collodion-charcoal immunoadsorbent which has resulted in extraction of circulating GBM antibody and attenuation or arrest of passively induced nephrotoxic glomerulonephritis. Adsorption of circulating porcine specific canine antibodies by extracorporeal perfusion of canine plasma through porcine kidneys has resulted in marked reduction of porcine specific antibodies and permitted the prolonged functional survival of a porcine renal xenograft perfused with whole canine blood. Extracorporeal immunoadsorption over immobilized Staphylococcus aureus -Cowans I has effected the removal of immune complexes and IgG in dogs with SLE. Similar perfusion of a dog with adenocarcinoma of the breast resulted in a marked gross and histologic regression of substantial tumor mass. C1q has been immobilized in collodion membranes and nylon wool and has demonstrated a capacity to extract immune complexes from the circulation of mongrel dogs. In addition, a chemotherapeutic program has been developed to effect the specific and sustained reduction of antibodies after extracorporeal immunoadsorption. We have now standardized several new radioimmunoassays to measure C1q binding, DNA binding and porcine-specific antibodies in the dog. The objective of the proposed experiments is to continue the longitudinal studies already begun of adenocarcinoma of the breast, SLE and hetrotransplantation with our newly developed immunoadsorbent. These studies will involve careful serological and immunohistochemical assessment of the total disease process. (Text Abridged.)

332. EXPERIMENTAL AND CLINICAL IMMUNOLOGY OF UROLOGIC CANCER

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The FANFT-induced bladder tumor in C3H/He mice was carried by subcutaneous inoculation in hind limbs of syngeneic animals. Challenge of previously immunized animals demonstrated the tumor to be immunogenic. Mice received hind limb inoculation of 10 to the 5th power viable tumor cells and were randomized into groups of 20. Treatment was begun either on the day of tumor inoculation (immunoprophylaxis, Group A) or when tumors measured 6 mm in diameter (immunotherapy, Group B). Weekly injections of C. parvum subcutaneously (SC), intraperitoneally (IP) or intralesionally (IL) significantly retarded tumor growth and increased survival in Groups A and B (p less than 0.05 compared to controls). BCG (Tice strain, 5 x 10 to the 4th power viable units) injected into the ipsilateral groin twice weekly retarded tumor growth slightly and increased survival significantly in both Groups A and B. Other routes of administration (SC, IP, IL and contralateral groin IM) and other dosage schedules of BCG were ineffective. Weekly injections of 1 mg of RNA extracted from spleens of tumor-immunized guinea pigs increased survival in Group A (p less than 0.05) but not tumor growth. Higher doses of RNA (3 or 4 mg) not only improved survival but inhibited growth in both Groups A and B. This was the first demonstration of inhibition of a growing, established tumor by immune RNA. Addition of the RNAase inhibitor, sodium dextran sulfate, increased tumor growth inhibition by RNA.

Chemoimmunotherapy experiments showed significant tumor inhibition with Cytoxan, 75 mg/kg, injected IP weekly (p less than 0.01), as well as increased survival (p less than 0.01). Combining Cytoxan with C. parvum IP or SC resulted in significantly greater (p less than 0.05) tumor growth inhibition and survival in both Groups A and B, than using either agent alone. Future experiments will include modification of BCG dosage regimen, treatment with various dosages of RNA to obtain a dose-response relationship, combination of RNA with tumor antigen, combination of RNA with Cytoxan, and exploration of the inhibitory effect of ipsilateral BCG injections.

4. MULTIMODAL AND OTHER THERAPEUTIC REGIMENS

333. THERAPEUTIC TRANSCATHETER ARTERIAL EMBOLIZATION IN MANAGEMENT OF MALIGNANT TUMORS

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OBJECTIVE: Transcatheter embolization is performed when occlusion of a blood vessel is desired. The rationale for surgical ligation of the tumor-feeding artery and percutaneous transcatheter embolization is the same but the latter is a much simpler and safer technique. We feel that embolization in cases of malignant disease helps by: 1. Reducing the vascularity of the tumor; 2. decreasing the viability of tumor cells so that inadvertent dissemination during surgical manipulation does not set up viable metastases; 3. reducing the tumor mass; 4. palliating local symptoms; 5. reducing tumor hormone production and 6. perhaps by triggering an increased immunological body reaction.

APPROACH: Following selective arterial catheterization and delineation of regional vascular anatomy, subselective catheterization of the desired vessel is performed, the position and stability of the catheter are verified and then a fractionated injection of the embolus made under fluoroscopic control. Following this an arteriogram is obtained for documentation. The usual substance we have used for embolization has been gelfoam and occasionally autoblood clot and barium.

PROGRESS: Renal cell carcinoma is the most commonly embolized malignant tumor in our series, hepatoma being the second most common. The majority of the patients have been operated upon following the embolization. The longest follow-up without surgery that we have observed so far, is for 1 year (ongoing) following diagnosis of a bilateral renal cell carcinoma. On the whole the results are encouraging.

334. LYMPHOGENOUS METASTASES OF RENAL CELL CANCERS

Hermanek, P., Sigel, A., Chlepas, S., Friedrich Alexander Universitat zu Erlangen Nurenberg, Surgical Clinic, *Maximiliansplatz, D8520 Erlangen, Federal Republic of Germany*

OBJECTIVE: The literature on the frequency of lymphogenous metastases with curable renal cell cancers varies considerably. This is at least partially due to different surgical techniques and different subtleties of the histological work-up. In nephrectomies for renal cell cancer with systematic retroperitoneal dissections, the objective is to determine frequency and topography of lymphatic metastases by means of exact histological examination.

APPROACH: As permitted by the patient's general condition and age, the nephrectomy for renal cell cancer is combined with a systematic bilateral lymph node dissection, which is carried out from the superior mesenteric artery to the inferior mesenteric artery and further distally in cases of positive nodes. The surgical specimens are marked at certain topographical fixed points. This is followed by histological examination of all lymph nodes with consideration of their localization. The lymph nodes are worked up with step sections. Relations to histological grade, stage, size and other parameters of the different malignancies are investigated.

PRESENT STATUS: So far (December 31, 1978) 87 systematic dissections have been examined: Regional lymph node metastases were found in 28 patients, i.e. 32%. Preliminary results have been published in 'Urologe' (Vol. 16, p. 208-212, 1977).

335. URINARY TRACT DYSFUNCTION IN WOMEN AFTER RADICAL HYSTERECTOMY AND LYMPHADENECTOMY

Kolstad, P., Asmussen, M., Radiumhospitalet, Dept. of Gynaecological Oncology, *Montebello, Oslo 3, Norway*

OBJECTIVE: A prospective study of urinary tract dysfunction after radical surgery for cervical cancer was assessed by utilizing simultaneously urethro-cystometry, radiological video filming, urinary flow measurement and isotope renography and ERPF (effective renal plasma flow).

APPROACH: Twenty-five women, who underwent radical surgery as the only treatment for cancer of the cervix, were examined with simultaneous urethro-cystometry, video filming, flow measurement, isotope renography and ERPF 1) before operation, 2) 2 weeks after operation, 3) one year after operation. All the patients were operated on by the same surgeon using a standardized technique.

Dysfunction such as paralytic bladder, altered bladder sensibility, residual urine, altered micturition pattern, altered urethral resistance, changes in the bladder capacity, changes in urethral and kidney function were all evaluated.

PROGRESS: Using the standard technique of radical hysterectomy and pelvic lymphadenectomy for treatment of cervical cancer at the Norwegian Radium Hospital, we find that the incidence of urinary tract dysfunction is low. The high incidence of long-term dysfunction in the urinary tract as described by several authors cannot be confirmed.

336. RADIOBIOLOGY OF NORMAL TISSUES

Withers, H. R., Peters, L. J., Meistrich, M. L., Dubravsky, N., Brock, W. A., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

We propose to pursue two broad objectives: an investigation of the pathobiology and dose-response relationships of the late effects of irradiation, and the quantitation of the responses of tissues to doses in a range used daily in clinical radiotherapy. Late effects will be studied in the lung, kidney, and testis, and low dose response relationships in the jejunum, kidney, and testis.

337. KIDNEY RESPONSE TO FRACTIONED RADIATION

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This research program will study the response of the rat kidney to fractionated irradiation. This study intends to provide information on the radiation tolerance of the kidney that will aid in the planning of optimal radiation therapy schedules.

Specifically, it will determine how the radiation tolerance of the kidney changes with fractionation, determine whether there are early indicators of kidney damage that correlate with late kidney damage, and determine whether non-lethal kidney damage is repaired between treatment courses 6 to 18 months apart. Information will also be gained concerning the slope of the dose-response curve for late radiation damage, and concerning optimal radiotherapy schedules.

Rats will receive bilateral kidney irradiations in several fractionation schedules, ranging from single doses to 32 fractions in 72 days. These irradiations are performed both with and without pentobarbital anesthesia. Animals will be followed for at least 18 months, with periodic determinations of blood pressure, blood chemistry, urine chemistry, and iodohippurate clearance times. Kidney doses will range from those producing only slight nephritis to those that will cause death within 12 months. Some of the animals surviving the first course of treatment will be given a second fractionated treatment 6 to 18 months later.

338. RADIATION THERAPY ONCOLOGY GROUP

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Radiation Oncology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The RTOG is a cooperative group of radiation therapy research and clinical centers organized for the purpose of conducting joint clinical investigations. The Division of Radiation Oncology of the University of Rochester Cancer Center is one of the member institutions of the RTOG and the Office of Protocol Design and of the Vice-Chairman are located within it. A listing of the major RTOG objectives and progress that has been made by the group, both nationally and at this institution, is described and includes: case accession, new research areas, standardized treatment planning, quality control, neutron clinical investigation, study registries and forms, and the interaction of the RTOG with other cooperative groups. The protocol design activities of the RTOG are reviewed through two schemes: First, major radiation themes which can apply to many disease sites: time dose factors, radiosensitizers, systemic irradiation, high LET irradiation, optimal time of radiation therapy and chemotherapy, hyperthermia, combining innovations in radiation therapy and mathemtical modeling; second, disease sites in terms of unique specific studies, especially studies of brain, lung, head and neck, genitourinary and metastatic disease. The activities of the Division of Radiation Oncology in protocol accession and the studies which are chaired by members of this institution are reviewed.

339. USE OF THE CELL SEPARATOR IN THE TREATMENT OF SELECTED CANCER PATIENTS

Hobbs, J. R., Forrest, D., Samman, P. D., Retsas, S., Melino, G., University of London, Westminster Medical School, Dept. of Chemical Pathology, *17 Page Street, London SW1P 2AR, England, United Kingdom*

APPROACH: Human neuroblastomas, melanomas, or hypernephromas are cultured and farmed for up to six generations. Tumor cells irradiated with 10,000 rads are injected into informed patient. Samples are later tested against the relative tissue culture, and also against the normal leukocytes of the donor of the tumor. This use of one haplotype-identical volunteer results in few reactions against the normal leukocytes of the patient. The reaction against the tumor cells is assayed to see whether it is mainly humoral or cellular: if cellular, the patient may be treated with irradiated lymphocytes harvested from the volunteer, or with transfer factor prepared from such lymphocytes, or indeed with extracts of RNA similarly prepared. If humoral, we harvest large quantities of plasma from the volunteer, process it over cold alcohol (COHN) to isolate the gammaglobulin fraction, to which either chlorambucil or rubidomycin is conjugated. Checks are made for sterility and pyrogenicity before use.

PROGRESS: Over 120 human volunteers have been immunized with no side effects so far, and in almost every case a usable immune reaction against the tumor. Therapy with immune cells has only been attempted in eight patients, all of whom were 'unblocked' prior to receiving the cells, and in all cases an objective regression of tumor was observed, but was nearly always temporary. Attempts to educate the leukocytes of the patient with extracts from the volunteer have so far failed (? any recipient clones).

Chemoimmunotherapy with 'tumor-specific antibodies' coupled to cytotoxic drugs has now been used in 10 Stage I patients, achieving impressive objective regression of tumor, but thus far transient up to 15 months.

340. PROTOCOL OF TREATMENT FOR NEPHROBLASTOMAS USING SURGERY, RADIOTHERAPY AND CHEMOTHERAPY - PHASE III

Lobo, J. F., Garcia, I., Piza, E. J., Camacho, M. A., Jimenez, E., Jimenez, B. R., Hospital Nacional de Ninos, Onco-Hematologia, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To establish value of 3 modes of treatment in relation to stage of tumor.

APPROACH: Histologic-surgical evaluation of degree of invasion, study of metastases and classification by stages. Use of actinomycin-D and vincristine at stage I; addition of radiotherapy with 60Co at stage II and III; and adriamycin at stage III and IV. (Controlled trial.)

PROGRESS: Twenty-five patients under study - 2 deaths. (Translated)

341. OMRF 7803 - ADVANCED METASTATIC RENAL CELL CARCINOMA (HYPERNEPHROMA) (HOD PLUS BCG TREATMENT REGIMEN)

Bottomley, R. H., Grozea, P. N., Hussein, K. K., Murray, J. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma,* 73104, United States of America

OBJECTIVES: To study the response of metastatic renal cell adenocarcinoma to combined hormonal therapy and chemotherapy with and without immunotherapy.

PLAN: Patients will be stratified according to performance status into two categories (grades 5-4 and grades 3-1). Treatment is with adriamycin every 3 weeks until a total dose of 450 mg/m2. Vincristine is given weekly for 5 treatments; then at 3-week intervals with adriamycin. Depo-Provera is given weekly. BCG is given every 2 weeks. Patients still in remission at the time of completion of their total dose of Adriamycin will receive maintenance with vincristine, BCG, and Depo-Provera. This maintenance regimen will be continued until relapse or complete response.

This study is still open. There are no V.A. patients on this study at this time.

342. CHEMOTHERAPY WITH ADJUNCTIVE C PARVUM IN METASTATIC HYPERNEPHROMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

343. RADIATION/CHEMOTHERAPY - GROWTH, STRUCTURAL AND FUNCTIONAL EFFECTS IN THE IMMATURE KIDNEY

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This project will investigate whether chemotherapy (actinomycin D, vincristine, adriamycin) and radiation, separately and in combination, modify normal and compensatory renal growth, structure and function in the weanling mouse. The interaction of single/combination chemotherapy (LD1, dose, I.P., in 5 daily injections) and single/multiple fraction irradiation (1000 rads, 750 rads, or fractionated equivalents in 5 daily fractions) will be studied in animals with two intact kidneys (normal renal growth) or in animals following unilateral nephrectomy (compensatory renal growth).

Weanling BLcF1 mice will be studied. Renal growth will be assessed by measurement of wet-dry kidney weight; renal morphology assessed by light and electron microscopy, and renal function estimated by measurement of serum BUN. Animals will be sacrificed at 3, 12, and 24 weeks following treatment.

This study will better define the morphologic and functional significance of radiation/chemotherapy-induced renal growth in immature mice; the radiation dose modifying effect of chemotherapy when combined with single/multiple fraction radiation; and the importance of sequence and timing of radiation/chemotherapy to the development of combined modality renal growth inhibition.

344. SOUTHWEST ONCOLOGY GROUP

Baker, L. H., Wayne State University, School of Medicine, Dept. of Oncology, *1014 Rivard, Detroit, Michigan,* 48207, United States of America

Wayne State University is the leading contributor of patients to Southwest Oncology Group protocols. In five of the thirteen committees of the group, Wayne State has contributed ten percent or more of the total population of patients studied by that group. These committees include: Brain (22%), GI (12%), GYN (10%), Lung (10%), Sarcoma (13%).

Wayne State University is represented on each disease committee of the adult division by member medical oncologists, pathologists, surgeons or radiation therapists.

Members of the department are chairing (or co-chairing) the following major southwest studies: Dr. Samson, 7817 testicular study; Dr. Baker, 7613 sarcoma study; Dr. Al-Sarraf, 7727/28 melanoma study; Dr. Samal, 7725 breast study; Dr. Buroker, new first line Phase II-III large bowel study. Other Phase II studies being chaired by faculty members include: Dr. Samson, 7611 Platinum in Sarcomas; Dr. Voravit, 7821 Maytansine in Lymphomas; Dr. Al-Sarraf, 7730 Platinum in Melanoma and 7716 Tamoxifen in Renal Cancer; Dr. Baker, 7870 Mitomycin and Bleomycin in Cervical Cancer.

The WSU faculty hold leadership roles in Southwest Oncology Group administration. Dr. Vaitkevicius and Dr. Buroker are Chairman and Vice-Chairman of the GI Committee, Dr. Baker is Chairman of the Sarcoma Committee, a member of the Executive Committee of the Adult Division, serves on the Steering Committee of GYN Committee and is a representative to the Pharmacology Committee.

BIBLIOGRAPHIC REFERENCES: Baker, L.H., Opipari, M.I., Wilson, H., Bottomley, R., and Coltman Jr., C.A. Mitomycin C, Vincristine and Bleomycin Therapy for Advanced Cervical Cancer. Obstetrics and Gynecology, 52: 146-150, 1978. Benjamin, R.S., Baker, L.H., O'Bryan, R.M., Moon, T.E., and Gottlieb, J.A. Chemotherapy for Metastatic Osteosarcoma - Studies by the M.D. Anderson Hospital and the Southwest Oncology Group. Cancer Treatment Reports 62: 237-238, 1978.

345. SOUTHWEST ONCOLOGY GROUP PROTOCOLS

Liepman, M. K., Bull, F. E., LoBuglio, A. F., Koller, C. A., Murray, E., Gabig, T., Dabich, L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *2215 Fuller Rd., Ann Arbor, Michigan,* 48105, United States of America

Protocol Titles: SWOG 7510 - Adjuvant Chemotherapy and Immunotherapy in Colon Cancer. SWOG 7634 - Chemotherapy of Colorectal Carcinoma. SWOG 7707 - Chemotherapy of Previously Treated Lymphoma Patients with Vincristine, BCNU, Adriamycin and Prednisone. SWOG 7719 -Chemotherapy of Previously Treated Myeloma Patients with VBAP (Vincristine, BCNU, Adriamycin and Prednisone) and DDP and Bleomycin. SWOG 7717 - Treatment of Patients with Adenocarcinoma of Unknown Primary. SWOG 7804 - Adjuvant Chemotherapy for Gastric Adenocarcinoma. SWOG 7738 - Chemotherapy of Pancreatic Carcinoma. SWOG 7814 - MTX vs. Cis-Platinum in Head and Neck Cancer. SWOG 7713/14 - CHOP vs. CHOP plus Levamisole vs. CHOP plus Levamisole plus BCG vs. COP plus Levamisole in Non-Hodgkin's Lymphoma. SWOG 7735 - Anguidine in Gastrointestinal Malignancies. SWOG 7716- Tamoxifen in Renal Cell Carcinoma. SWOG 7639 - Chemotherapy of Gastric Adenocarcinoma. SWOG 7803 - Baker's Antifol in Advanced Renal Cell Carcinoma.

These are multi-institutional cooperative group trials of single agents and combination therapy in the management of selected cancers and hematologic malignancies.

346. EASTERN COOPERATIVE ONCOLOGY GROUP STUDIES

Falkson, G., Falkson, H. C., van Dyk, J. J., van Eden, E. B., Portugal, M. A., Fourie, L. S., van der Merwe, A. M., Smit, J. E., Pretorius, F. J., Steenkamp, S. M., Howard, M., Mallet, L., University of Pretoria, Dept. of Cancer Chemotherapy, *P.O. Box 667, Pretoria, Transvaal, South Africa*

This application is for a continuation grant for prospective randomized cooperative clinical trials under the aegis of the Eastern Cooperative Oncology Group. The goals are to improve diagnostic procedures and treatment for patients with cancer. The aim is to study new agents, new agent combinations and new treatment schedules in order to gain better disease control. The effort will be directed towards delineation of effective treatments, and their application. Such treatment will emphasize multimodality inter-disciplinary management (with Internal Medicine, Pathology, Surgery and Radiotherapy). Participation in all the protocols developed by ECOG is envisaged. The principal investigator is at present Co-chairman and will be Chairman of the Breast Cancer Committee of ECOG for 1981/82 with all the responsibility associated therewith. He is also Chairman of the Breast Cancer Studies EST 2177 and EST 1179. The principal investigator is Chairman of the studies of Primary Liver Cancer EST 2273 and EST 1279 and continues to run pilot studies on Primary Liver Cancer. He is also Co-chairman of EST 1277 for Colon Cancer. Continued participation in studies of gastrointestinal, lung, hemopoietic, gynecological and genitourinary cancer as well as sarcoma and malignant melanoma is aimed at. Special attention will be paid to mesothelioma for which a protocol has been submitted. An expanded role in the development of new protocols is envisaged. Improved patient care and improved education at the University of Pretoria will result.

BIBLIOGRAPHIC REFERENCES: Chiuten, D.F., Bennett, J.M., Creech, R.H., Glick, J., Falkson, G., Brodovsky, H.S., Begg, C.B., Muggia, F.M., and Carbone, P.P. VM-26, a New Anticancer Drug with Effectiveness in Malignant Lymphoma: An Eastern Cooperative Oncology Group Study. (EST 1474). Cancer Treatment Reports 63: 7-11, 1979. Portugal, M.A., Falkson, H.C., Stevens, K. and Falkson, G. Acute Leukemia as a Complication of Long-Term Treatment of Advanced Breast Cancer. Cancer Treatment Reports 63: 177-181, 1979.

347. CANCER CENTER SUPPORT - COMPREHENSIVE

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The Wisconsin Clinical Cancer Center is a University-based comprehensive cancer center dedicated to patient oriented laboratory and clinical cancer research, multidisciplinary care, and professional and public education. The WCC has an academic home in the Medical School and Center for Health Sciences with 45 professional members in the Department of Human Oncology. The Center also serves as a focal point for cancer research and patient care for other departments in the Medical School, providing financial, intellectual, and physical facilities for a large number of associate members. A close relationship exists with these other departments in regard to cancer activities.

The WCCC is responsible for major clinical research programs with multidisciplinary trials for breast, pancreas, lung, melanoma, and genitourinary cancers. Laboratory research programs include etiology, pharmacology, radiobiology, endocrinology, immunology and genetics. Outreach programs include many professional and non-professional educational activities, as well as diagnostic and management networks for colposcopy and head and neck cancer. Future ares of emphasis will include strengthening of current programs, as well as development of new effforts in somatic cell genetics, nutrition and preventive oncology.

348. THE COST OF TREATING GASTROINTESTINAL AND URINARY TRACT CANCER

Brown, S., University of Cincinnati, School of Medicine, Dept. of Hematology, *Eden & Bethesda Aves., Cincinnati, Ohio*, 45221, United States of America

OBJECTIVE: To determine the cost of treating gastrointestinal and urinary tract cancer.

APPROACH: Case studies of various types of gastrointestinal and urinary tract cancers are being selected and costs determined.

PROGRESS: Limited results indicate that these costs can be determined systematically. Approximately 20 cases of various types have been examined.

349. URETERAL REIMPLANTATION (DOGS)

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This is part of a broader project. A summary of this subproject is not available.

350. URETHRAL RECONSTRUCTION-SURGICAL PROCEDURE (DOGS)

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This is part of a broader project. A summary of this subproject is not available.

351. URETERAL SUBSTITUTION WITH PLASTICS (DOGS)

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This is part of a broader project. A summary of this subproject is not available.

IV. OTHER BIOLOGY AND PATHOLOGY OF RENAL AND UROLOGICAL CANCER

352. STEROID HORMONE RECEPTORS IN HUMAN HORMONE-SENSITIVE TUMORS

Galli, M. C., DeGiovanni, C., Grilli, S., Universita degli Studi di Bologna, Istituto di Cancerologia, *via S. Giacomo 14, 40126 Bologna, Italy*

OBJECTIVE: To test a correlation between the presence of estrogen, androgen, progestin and/or glucocorticoid receptors in human hormone-sensitive tumors and the response rate to endocrine treatment.

APPROACH: Cytoplasmic steroid receptors are determined using a slightly modified dextan-coated charcoal (DCC) method (Cancer Lett. 2, 247-158, 1977; IRCS Med. Sci., 6, 418, 1978) in breast, prostate, endometrium, kidney and ovary cancer and related normal tissues. Hormonal plasma levels and histochemical parameters such as: grading, elastosis, casein production, etc., are determined and clinical data are collected.

PROGRESS: Up to now steroid hormone receptors have been determined in about 200 breast specimens, 50 prostate specimens, 100 endometrial biopsies and 20 cases of kidney tumor and 20 cases of ovary neoplasm. Interestingly, estrogen, androgen, progestin and glucocorticoid receptors are present also in normal and neoplastic ovary.

353. ETIOLOGY OF AN INHERITABLE RAT RENAL TUMOR

Eker, P., Kotlar, H. K., Sanner, T., Norsk Hydro's Inst. for Cancer Research, Radiumhospitalet, Dept. of Biochemistry, *Montebello, Oslo 3, Norway*

OBJECTIVE: To study the role of RNA tumor viruses and different immunological and biochemical factors involved in the development of an inheritable renal tumor in an inbred rat strain.

APPROACH: The present investigation is carried out on an inbred strain of rats with renal tumors (Tw). These rats, originating from Wistar rats, develop multiple, bilateral tumors of varying size. Occasionally, the tumors show metastatic spread. The tumors are inherited in a pattern consistent with a

single autosomal lethal gene. Biochemical studies suggest that cyclic nucleotides may be involved in the development of the tumors. Immunological factors will be studied with the use of leukocyte adherence inhibition (LAI) assay. Preliminary electron-microscopic studies on in vitro cultures of the tumor suggest the presence of particles similar to C-virus. In further studies attempts will be made to identify the role of the viruses in the development of the tumor.

354. STEROL METABOLISM IN HUMAN RENAL CANCER

Gonzalez, R., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Surgery, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The purpose of this research project is to determine the causes and mechanisms of cholesterol accumulation in human cancer of the kidney. We are using cultured human kidney cells - normal and malignant. Cholesterol accumulation is a unique characteristic of specific human kidney tumors; we hope these studies will offer new insights regarding the treatment and detection of these tumors.

355. HORMONAL EFFECTS ON RENAL METABOLISM

Davis, B. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *915 N. Grand Blvd., St. Louis, Missouri*, 63106, United States of America

The major purpose during the past year has been to investigate cooxidation of urinary bladder carcinogens by prostaglandin endoperoxide synthetase (PES) from the renal medulla. Cooxidation was studied using microsomes from the inner medulla and evaluating the effects of specific substrates and inhibitors of prostaglandin endoperoxide synthetase on metabolism by those microsomes of benzidine and FANFT. Radiochemical techniques and spectrophotometric techniques were used to evaluate substrate metabolism. Additional studies were performed using a whole cell preparation, the renal slices. PES was shown to cooxidize both FANFT and its in vivo metabolic product ANFT. That metabolism was related to the hydroperoxidase rather than the cyclooxygenase component of PES. Hydroperoxidase metabolism of benzidine was also documented. The metabolism of benzidine by PES resulted in the activation of the benzidine to a compound which reacted with and formed a covalent bond with nucleic acids. Furthermore, benzidine was found to be metabolized by inner medullary slices of the rabbit kidney. That slice metabolism also was by a process of cooxidation by PES and resulted in a compound which was covalently bound to tissue proteins. On the basis of the results, an in vivo experiment was designed and is in progress. That experiment will test the capacity of inhibitors of PEC to reduce or eliminate the capacity of feeding a diet containing 0.2% FANFT to induce urinary bladder cancer in rats.

356. HUMAN RENAL CELL CARCINOMA IN VIVO (NUDE MOUSE) AND IN VITRO

Kistler, G. S., Peter, H. J., Groscurth, P. Universitat Zurich, Dept. of Anatomy, *Gloriastr. 19, CH8006 Zurich, Switzerland*

OBJECTIVE: To investigate: 1) The factors influencing the transplantability of human renal cell carcinomas in nu/nu mice, 2) the morphological, immunological and biochemical characteristics of the tumors during long-term transplantation and 3) to establish tumor cell lines for in vitro experimentation.

APPROACH: Fragments of renal cell carcinomas (surgical specimens) are implanted subcutaneously into nu/nu mice. Growing tumors are serially transplanted and checked for various morphological, immunological and biochemical parameters. Nu/nu mouse-grown tumors are used for establishing pure tumor cell lines.

CURRENT STATE OF THE PROJECT: Up to now, only one out of 18 renal cell carcinomas could be serially transplanted in nude mice. The transplants maintained their morphological characteristics up to the 40th in vivo passage. Tumor cells isolated from the transplants could be established as a cell line which has reached its 79th in vitro passage. Preliminary reports have been published.

357. CHARACTERIZATION OF POTENTIALLY AUTOANTIGENIC AND COMPLEMENT ACTIVATING CYTOSKELETAL FILAMENTS IN RENAL AND MAMMARY CARCINOMAS

Linder, E., Miettinen, A., Holthofer, H., University of Helsinki, Dept. of Bacteriology & Immunology, *Haartmaninkatu 3, SF00290 Helsinki 29, Finland*

The study is based on the observation that about 15 percent of patients with renal carcinomas have circulating antibodies which in vitro react with cytoplasmic intermediate (10 nm) filaments of cultured cells. Preliminary studies have indicated that targets for their autoimmune response reside in the tumor tissue. Our interest in these filaments in further based on the observation that they have the capacity to bind and activate complement. Both autoantibodies and complement components C1q, C4 and C3 have been used as immunohistological markers at the cellular and at the tissue level. The purpose of the research project is to study the occurrence and tissue distribution of intermediate filaments in renal and mammary carcinomas using patient autoantibodies, experimental antisera against cytoskeletal filaments and serum complement as immunohistological markers. Other markers employed are antibodies against collagen, fibronectin and amyloid P-component, anti-clotting factor VIII, and fluorescent lectins. Preliminary results regarding renal carcinomas indicate that intermediate filaments of the tumor vasculature react with patient autoantibodies and may cause antibody-independent complement activation.

358. SERUM ENZYME ALTERATIONS IN RENAL NECROSIS (DOGS)

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This is part of a broader project. A summary of this subproject is not available.

359. RNA METHYLATION - A PARADOX IN NORMAL AND CANCER CELLS

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The sequence of 5.8S ribosomal RNA has recently been established in several mammalian species including man. One position in the sequence contains a partial 2'-O-methylation which occurs in lower yields in tumor cells. The percent -UmG- was found to vary from 17 to 72% when examined in a variety of tumor and normal tissues, yet another methylated position, -GmC-, remained constant at 100% (1 molar yield). The role of methylation is not yet clear; however; it appears to be important for normal processing of ribosomal RNA. Recent work has also shown that transfer RNA methylation is reduced in tumor cells (both cytoplasmic and mitochondrial tRNA) suggesting a general phenomenon of undermethylation in cancer cells. In contrast to the in vivo undermethylation of RNA, the methylase activity for both base methylation in tRNA and ribose methylation in RNA appears to be elevated when measured in vitro. Tumor cells may produce excess enzyme in an attempt to compensate for the low methylation levels, but because of inhibition or lack of substrate, S-adenosyl-methionine (SAM), this has no effect.

Through a study of the in vivo and in vitro methylation of ribosomal RNA at specific sequences, the paradox of low RNA methylation and elevated methylase activities in tumor cells may be explained. Primary cultures of rat kidney cells, the normal rat kidney (NRK) cell line, NRK cells transformed by wild-type mouse sarcoma virus (MSV), or a temperature-sensitive (ts) transformation mutant of MSV, and a ts mutant of baby hamster kidney cells unable to process rRNA, will be used to examine the effect of culture conditions such as growth rate, passage number, and methionine concentration on methylation. The levels of SAM, S-adenosylhomocysteine, and methionine transport will be monitored and compared to ribosomal RNA methylation and methylase activities in these cells. An enzyme assay for the methylation of the specific -UmG-position in 5.8S rRNA will be developed and will be useful in attempts to purify the enzyme and to determine the part of the sequence and structure of 5.8S rRNA necessary for enzyme recognition.

360. OER AND RBE OF HELIUM ION BEAM IN HUMAN KIDNEY CELLS

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This is part of a broader project. A summary of this subproject is not available.

361. RENAL METABOLISM OF BETA-2 MICROGLOBULIN

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The renal metabolism of beta-2 microglobulin (B2M) will be evaluated in patients with various types of renal disease and carcinoma. In addition, experimental animal studies will be conducted. Dogs will be used to study the renal handling of B2M as affected by variations in renal blood flow, glomerular filtration rate and tubular metabolism under controlled conditions. The relationship of the filtered load of B2M to urinary excretion will be measured in patients with various renal diseases and carcinoma. Multiple large and small proteins will be measured, including IgA, IgG, IgM, lysozyme and B2M to determine the relative filterability of B2M with various disorders of glomerular permeability and tubular metabolism. The methods to be used will be those of standard immunologic, immunodiffusion and radioactive immunoassays for those proteins listed above, with the exception of lysozyme where the lysoplate method of Osserman will be utilized. The animal studies will be conducted as acute experiments using dogs with continuous steady state perfusion experiments, evaluating the variations in renal blood flow, glomerular filtration rate and filtration fraction induced by various drugs and physiologic alterations; loading with species specific L-chains and A2 microglobulin in addition to B2M will be evaluated with respect to renal uptake of these proteins. Variation in B2M isoprotein excretion in the urine will be evaluated, particularly in patients with various types of carcinoma.

BIBLIOGRAPHIC REFERENCES: Hall, P.W. and Dammin, G.J. Balkan nephropathy. Nephron (in press) 1978. Vacca, Christina V., Hall, Philip W. and Crowley, Andrea Q. Preparative electrofocusing in the isolation and purification of human Beta-2 Microglobulin. Electrofocusing, 1978. LKB Laboratories (in press).

362. CLINICAL PATHOLOGY OF RENAL TUMORS

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We are trying to complete the follow-up on adenomas, sarcomas of the kidney and adult Wilms' tumors. The histological study has been completed. We are waiting for clinicopathological correlation.

Some of the studies have been included in a chapter on kidney to be published in the forthcoming year.

363. HISTOPATHOLOGY OF END-STAGE AND DIALYSIS KIDNEYS

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Previous studies described in 6 articles (3 published, 3 in press) and 2 abstracts document pathologic changes in 'end-stage'/dialysis kidneys that require further work and explanation. The morphologic findings may contribute to the understanding of pathophysiologic problems encountered in the management of renal failure patients and to basic knowledge regarding the relationships of cells that comprise kidney tissue. Electron microscopy, enzyme histochemistry, immunohistochemistry, and morphometry are planned to complement the continued histological and histochemical study of dialysis kidneys. Multiple tissue blocks and serial histological sections will allow the examination and reconstruction of entire structures or units (i.e. renal lobules) of kidney tissue. Emphasis in future investigations will be placed upon: 1. Pathological changes in the juxtaglomerular complex and renal medulla. 2. Metaplastic transformation of the renal interstitium. 3. Neoplastic and metaplastic transformations of the glomerular and tubular epithelium.

364. ETIOLOGY OF UROLOGIC NEOPLASIA

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PURPOSE: To characterize some of the steps in chemical carcinogen-induced neoplastic change, using cells from various urologic tissues.

METHODS: Human kidney epithelial cells are from the non-tumor portion of kidneys removed from kidney cancer patients. Urothelial cells are from swine bladders from a local abbatoir or from bladders from dogs killed in other research projects. Cells in culture are treated with carcinogens and studied for change in growth, morphology, intercellular relations, anchorage-independent growth, and formation of tumor in athymic mice; and for induction of DNA-repair synthesis, chromosome damage, DNA strand breaks, sister chromatid exchanges, and somatic mutation.

RESULTS: The kidney and bladder cells grow routinely in monolayer culture and can be passed several times. We have determined toxic levels of several carcinogens, including N-methyl-N-nitrosourea (MNU), 4-nitroquinoline-1-oxide (NQO), cyclohexylamine (CHA), and aflatoxin Bl (AFL). NQO and MNU enhance long-term growth in swine urothelial cells, and CHA appears to have that effect on canine cells. NQO causes some morphologic change in human kidney cells. NQO causes chromosome damage in swine urothelial cells, and induces DNA-repair synthesis. MNU also induces DNA-repair synthesis. By extending and correlating these studies, we expect to gain valuable insight into the intermediate steps in the carcinogenic process.

BIBLIOGRAPHIC REFERENCES: Y. Sharief, C.F. Reich, D.D. Mickey, R.A. Bonar: Cytogenetic Study of a Human Tumor Cell Population in Vitro and in Athymic 'Nude' Mice. Genetics 91: 115-116, 1979.

365. PLASMA MEMBRANE OF NORMAL AND NEOPLASTIC UROTHELIA

Bonneville, M. A., Caruthers, J. M., University of Colorado, Boulder Campus, School of Arts & Sciences, Dept. of Molecular, Cellular & Developmental Biology, *1200 University Ave., Boulder, Colorado*, 80302, United States of America

The immediate goal of this proposal is to define ultrastructurally the cytoskeleton of the specialized superficial lumenal cells of the mammalian urothelium. This knowledge will be applied to our overall objective which is to describe the early cellular changes relevant to the process of carcinogenesis. The intact, as well as extracted, epithelium will be examined by transmission electron microscopy to determine the types of cytoplasmic filaments and their relationship to the plasma membrane, the junctional complex and to specific cytoplasmic vesicles. These preparations will also be examined with high-voltage electron microscopy in order to describe from stereoscopic images the three-dimensional organization of the cytoplasm under normal conditions. These studies will form the basis for describing the cytoskeleton in cells derived from urothelial tissues poised at progressive stages of chemically induced carcinogenesis.

BIBLIOGRAPHIC REFERENCES: J.M.S. Caruthers and M.A. Bonneville. 1979. Interaction of antibodies to sheep urothelial plaque regions with the lumenal plasma membranes of other mammals. Urol. Res., in press. Caruthers, J.M.S. and M.A. Bonneville. 1979. Comparative parameters in the isolation of lumenal plasma membranes from sheep urothelia. Biol. Cell. in press.

366. THE INVASIVENESS OF TUMORS AND THEIR ABILITY TO FORM BONE METASTASES

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OBJECTIVE: To relate the prostaglandins formed by human lung, kidney and prostate tumors to their invasiveness and ability to form bone metastases.

APPROACH: Tumors removed at operation will be extracted for prostaglandins and bioassayed. The patients will undergo skeletal scintigraphy in the pre- or post-operative period, and again at yearly intervals. The production of prostaglandins

by the tumors will be correlated with these findings, with histology, and patient survival.

367. RENIN PRODUCING CONGENITAL MESOBLASTIC NEPHROMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

368. RIBONUCLEOPROTEIN COMPLEXES IN RENAL CARCINOMA

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The equilibrium between unassociated (ribosome-free) cytoplasmic messenger ribonucleoprotein (mRNP) and polysome-associated mRNP is likely to be a key step in the translational control of cell proliferation. Therefore, the relative amounts and kinetics of these classes of mRNP and their nuclear precursors (hnRNP) will be studied in an organ (the kidney) that can be made to show graded responses from hypertrophy to hyperplasia to neoplasia. Renal hypertrophy will be produced by contralateral nephrectomy, hyperplasia by injection of folic acid, and neoplasia by dimethylnitrosamine treatment of Charles River mice. Particular attention will be paid to homologies in the protein components of the RNPs as assessed by labeling and by two-dimensional gel electrophoresis and the kinetics of labeling the integral RNA which may indicate precursor-product relationships. These proteins may stabilize the RNPs during stimulated growth and modulate the processing and translation of their RNAs; other work in this laboratory strongly suggests that the rate of degradation of protein and ribosomal RNA, rather than the rate of synthesis, is a major controlling mechanism in renal growth. The relative efficiencies of isolated RNP complexes in total protein synthesis will be measured in a cell-free protein synthesizing system and compared to that of deproteinized poly(A)-containing mRNA and reconstituted RNP systems. We propose to show that RNP complexes isolated during different patterns of growth contain some differences in their protein complements, that these differences are directly related to the control of mRNA expression and that these proteins determine the distribution of mRNA between translating and non-translating states.

369. BIOLOGICAL ROLES OF SERUM AND CELL FACTORS - CONTROL OF THE CELL CYCLE

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The research to be carried out in this project is concerned with the biological role of a kidney epithelial cell growth inhibitor. The growth inhibitor is isolated from the culture medium of BSC-1 cells, kidney epithelial cells of African green monkey origin. Inhibitors play a major role in density-dependent regulation of growth of this epithelial cell line. The purified growth inhibitor is active 1 ng/ml. It appears to be a highly specific inhibitor of kidney epithelial cell growth in cell culture. The specific aim of this project is to study the action of this kidney epithelial cell growth inhibitor in vivo in newborn mice.

370. IMMUNOLOGIC MECHANISMS IN RENAL DISEASES IN CHILDHOOD

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This is a comprehensive program to study the immunopathogenesis of renal disease. C3 nephritic factor will be examined by a structural approach and its production in animals will be attempted. Prevention of lupus nephritis in NZB/W mice and its treatment will be pursued with tolerogens to DNA and corticosteroids. Strain differences in rats following induction of autologous immune complex nephritis will be related to differences in T cell subsets and T cell suppressor activity. Malignant transitional epithelium will be examined for synthesis of C1q, the first component of complement. Ultrastructure of glomeruli will be studied in normal and nephritic rats.

BIBLIOGRAPHIC REFERENCES: Levey, R. H., Parkman, R., Rappeport, J., Nathan, D.G. and Rosen, F.S. Successful bone marrow transplantation in sensitized recipients. Transpl. Proc. 11:199-204, 1979. Rutenberg, W.D., al-Khalidi, U., Rosen, F.S. and Merler, E. Purification and biochemical characterization of human lymphocyte mitogenic factor (LMF). J. Immunol. 122:723-727, 1979.

371. IN VITRO GROWTH OF NORMAL KIDNEY AND BLADDER EPITHELIUM

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Work on the characterization, transformation and cell hybridization of epithelium has been hampered by the difficulty of obtaining pure normal epithelium in quantity. Although normal epithelium can be maintained in explant cultures, these invariably contain large numbers of mesenchymal cells. This is a particular problem in the bladder where epithelium forms a very small proportion of the total cell mass. Several methods suggested for the inhibition of growth of fibroblasts have been unsuccessful in our hands but Taub et al. (Proceedings of the National Academy of Sciences 1979, 76, 3338) reported that a dog kidney cell line and mouse kidney epithelium in primary culture could be maintained in a chemically defined medium supplemented with insulin, transferrin, prostaglandin E1, hydrocortisone and triiodothyronine. We have confirmed their observation that predominantly epithelial explant cultures can be maintained for up to 10 days in this medium, whereas cultures in serum-supplemented medium are rapidly overgrown by mesenchymal cells. Unfortunately bladder epithelium does not behave in this way in the chemically defined medium. For the adult bladder we use a prolonged enzyme digestion technique similar to that used by Hodges and co-workers (see ICRF Scientific Report 1978 - report 141). By microdissection epithelium can then be removed from adult mouse or human embryo bladder and single cell suspensions prepared. These can be plated in standard tissue culture dishes and survive for 5 days or more. The separated kidney and bladder epithelia have been used for transformation, gel analysis and cell hybridization experiments described in later reports.

372. GROWTH, NUTRITION, AND NEOPLASTIC TRANSFORMATION OF MAMMALIAN CELLS IN VITRO

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The long-term objective of this program is to understand the mechanism(s) of neoplastic transformation in cultured mammalian cells, particularly human cells. Studies described address two intermediate goals: (a) the role of calcium and dissolved oxygen on survival, proliferation, and differentiated function; and (b) the induction of cellular injury after cell exposure to low-intensity visible light. In studies to date, a lowered calcium concentration appears to retard differentiation of human epithelial cells in that squame formation is not observed; unlike the mouse epithelial system, however, proliferation is not enhanced by lowering calcium concentration. In addition, human skin and monkey kidney cells exhibit a critical oxygen requirement for attachment and proliferation, and monkey kidney cells use oxygen more rapidly than fibroblasts at the same cell density. This rapid utilization affects proliferation and functional responses. Visible light causes chromatid damage in normal human fibroblasts. A medium-specific, cell-type specific cell killing is observed when fibroblasts are exposed to light in medium NCTC 168, a response mediated by hydrogen peroxide products during light exposure.

BIBLIOGRAPHIC REFERENCES: Parshad, R., Sanford, K.K., Taylor, W.G., Tarone, R.E., Jones, G.M., and Baeck, A.E.: Effect of intensity and wavelength of fluorescent light on chromosome damage in cultured cells. Photochem. Photobiol. 29: 971-975, 1979. Price, F.M., Camalier, R.F., Gantt, R., Taylor, W.G., Smith, G.M., and Sanford, K.K.: A new culture medium for human skin epithelial cells. In Vitro 16: 147-158, 1980.

373. FACTORS REQUIRED FOR MAMMALIAN CELL DIVISION

Holley, R. W., Salk Inst. for Biological Studies, Molecular Biology Laboratory, *10010 N. Torry Pines Blvd., P.O. Box 1809, San Diego, California*, 92112, United States of America

The long-range objective is to understand enough about the factors that control mammalian cell growth to be able to apply this knowledge to the control of malignant growth. As a result of recent work, a broad picture is now available of the control of growth of mammalian cells. Application of this knowledge requires additional information and experimentation. Detailed information is needed of the specific factors that control the growth of the epithelial cells that are most important in the origin of tumors, in order to design rational procedures to restrict tumor growth. It is important to know whether these epithelial cells produce inhibitors of their own growth, such as the growth inhibitors that are produced by kidney epithelial cells. Isolation of the kidney determines whether the inhibitors can be used to restrict the growth of kidney tumors. These questions will be studied using methods of cell culture to investigate growth controls, using ultrafiltration, chromatography and other biochemical procedures in the isolation of the inhibitors, and using cell free systems, cell culture and work in intact animals to investigate the properties of the inhibitors.

BIBLIOGRAPHIC REFERENCES: Holley, Robert W. Control of growth of kidney epithelial cells. IN Control Mechanisms in Animal Cells, edited by L. Jimenez de Asua et al., Raven Press, New York, pp. 15-25, 1980. Holley, Robert W., P. Bohlen, R. Fava, J. H. Bladwin, G. Kleeman and R. Armour. Purification of kidney epithelial cell growth inhibitors. Proc. Natl. Acad. Sci USA 77, 5989-5992 (1980).

374. FUNCTION AND GROWTH OF A KIDNEY EPITHELIAL CELL LINE

Saier, M. H., University of California, San Diego Campus, Graduate School, Dept. of Biology, *P.O. Box 109, La Jolla, California*, 92037, United States of America

The vast majority of human cancers are carcinomas, yet little is known regarding the factors controlling epithelial cell growth. Similarly, the mechanism of in vitro malignant transformation of differentiated epithelial cells by chemical carcinogens is poorly understood. In order to correct this deficiency we have initiated studies to define (a) the differentiated properties of an epithelial cell line of dog kidney origin (MDCK) (b) the in vitro growth properties of these cells and (c) the growth properties of the MDCK cells in an immunosuppressed host animal, the athymic 'nude' mouse. Our previous studies have suggested that the nude mouse can be used reliably to evaluate the tumorigenicity of established cell lines and that the growth parameters measured in tissue culture do not correlate consistently with tumorigenic potential for a variety of heterologous cell lines.

As part of a long-range program aimed at defining the molecular events accompanying neoplastic transformation of a single selected epithelial cell line, we propose to: 1) Further establish the differentiated transport and regulatory properties of the MDCK cells. 2) Continue our studies aimed at determining the in vitro growth requirements of the MDCK cells in serum-free medium. 3) Obtain transformed variants of the MDCK cells following exposure to selected chemical carcinogens. 4) Establish a causal relationship between modification of in vitro growth dependency and neoplastic transformation.

375. CONTROL OF KIDNEY CELL GROWTH

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The objective of the applicant's research has been to elucidate biochemical mechanisms which initiate and regulate renal growth in physiological and pathological states. The approach used in these studies has been to characterize the biochemical and ultrastructural correlates of kidney growth in three model systems: compensatory growth after uninephrectomy, regeneration after toxin-mediated necrosis, and growth induced by systemic potassium depletion. An attempt has been made to identify serum factors, nutrients (amino acids), and ions (potassium) as extracellular and intracellular modifiers of cell growth. These investigations have been carried out in slices and broken-cell homogenates of rodent kidney.

The purpose of the proposed year of study is to acquire training and experience with cultured renal cells to bridge the gap between work on growth control in cell culture and work in the intact animal. The applicant will work in the Cell Biology Laboratory of Dr. Robert W. Holley at the Salk Institute for Biological Studies in San Diego, California. Studies will be performed in vivo and in vitro to further define the role of serum factors, low molecular weight nutrients, and ions on the growth of cultured renal cells of the BSC-1 line and of different zones of the rodent kidney.

376. BEHAVIOR OF ADULT UROTHELIUM IN CONTACT WITH DIFFERENT SUBSTRATES

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The work on the interaction of normal adult urothelium with different substrates has been extended to include a number of viable and inert substrates. On the basis of cytodifferentiation as determined by urothelial cell surface topography it has been shown that when urothelium is recombined with homotypic stroma immediately after separation a normal differentiation pattern of behavior is retained over long periods of culture. If either urothelium or stroma are aged independently and then recombined at different time intervals urothelial growth occurs but cytodifferentiation is abnormal - with aged urothelium no cytodifferentiation is observed and with aged stroma a hyperplastic response occurs with the cell surface topography showing numerous microvilli. When urothelium is combined with components of the normal stroma, i.e., lamina propria and muscle, growth is observed but cytodifferentiation is abnormal in the urothelium-muscle recombinant, whereas in the urothelium lamina propria combination growth and cytodifferentiation follow the normal pattern. Both growth and cytodifferentiation can be shown to be altered by inert substrates such as collagen gel, collagen coated millipore, thermanox coverslips and cellulose acetate.

377. IN SITU FREEZING OF PORTIONS OF THE KIDNEY (RABBITS)

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This is part of a broader project. A summary of this subproject is not available.

V. IMMUNOLOGICAL STUDIES OF BLADDER CANCER

378. SERIAL IMMUNOLOGICAL STUDIES ON BLADDER CANCER PATIENTS

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OBJECTIVE: To establish the relationship, if any, between changes in immune status and clinical course in patients with bladder cancer.

APPROACH: Thirty patients with histologically proven transitional cell carcinoma of the bladder have been included in the study. All were under 70 yrs of age at presentation and have been fully assessed in terms of clinical staging before treatment. Primary treatment has been by megavoltage irradiation of the tumor and surrounding tissue.

Blood is drawn from the patients before treatment, during and at the end of the course of radiotherapy and thereafter at approximately 3-month intervals for at least 3 yrs or until death. From each sample a total and differential white cell count is made, lymphocytes are separated and the percentage of 'E' rosette-forming cells (T cells) is recorded. Serum and lymphocytes are then stored in liquid nitrogen. Serial samples of cells from a given patient are recovered at a later stage and tested simultaneously for in vitro response to a range of soluble and cellular mitogens.

PROGRESS: Four patients have completed 3 yrs follow-up and an additional eight patients have been in the study for more than 2 yrs. Preliminary analysis of serial lymphocyte counts is now being undertaken in relation to clinical and histo-

logical staging of tumors and in relation to survival time. Thirteen patients have died from the disease, all except one within 2 yrs of presentation.

379. CELLULAR IMMUNE RESPONSES TO HUMAN BLADDER CARCINOMA

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It is known that the cellular immune response plays a role in slowing the progression and spread of neoplasms in experimental animals, but this has not been proven in man. The objectives of our research are to investigate and determine the relationship between cellular immune responses, both tumor specific and general, and the biological behavior of bladder carcinoma. Specifically, we propose to continue our studies to determine whether bladder cancer patients have T-lymphocytes cytotoxic for tumor cells in vitro, whether this cytotoxicity is malignancy related, whether there is a genetic restriction to this cytotoxic T-cell reactivity, whether patients with bladder carcinoma have antigen specific and/or genetically restricted suppressor cells, and to determine the relationship of the major histocompatibility complex (HLA) antigens to these phenomena and to the incidence and biological behavior of bladder carcinomas.

BIBLIOGRAPHIC REFERENCES: Bean, M.A., Akiyama, M. and Brankovan, V. Tumor induced suppression of mixed leukocyte culture response (MLR) in humans. In press. Abstract, Fourth International Congress of Immunology, July 21-26, 1980. Akiyama, M., Bean, M.A., Brankovan, V. and Anderson, R.P. Suppression of the mixed leukocyte culture (MLC) response of cancer patients triggered by contact with autologous tumor cells. In press. Proceedings American Association of Cancer Research, Vol. 21, 1980.

380. SUPPRESSOR CELL ACTIVITY IN BLADDER CANCER PATIENTS

Catalona, W. J., Ratliff, T. L., Jewish Hospital of St. Louis, *216 S. Kingshighway Blvd., St. Louis, Missouri,* 63110, United States of America

We developed a reproducible assay for the measurement of concanavalin A (Con A)-inducible suppressor cells. Using this assay system we studied suppressor cell activity of peripheral blood lymphocytes (PBL) from urologic cancer and control patients. Although lymphocyte proliferation to Con A was depressed in many of the cancer patients, no difference in suppressor cell activity between cancer and control patients was observed. These results suggest that suppressor cells of the type induced by Con A are not responsible for the immunosuppression observed in urologic cancer patients.

We found that protein A from Staphylococcus aureus (SpA) induced Type II interferon production in human PBL. Maximum interferon production was observed 24 hours after treatment with SpA. Moreover, unlike other mitogen interferon inducers, induction of interferon was enhanced by macrophage depletion. Cell fractionation studies showed that the interferon-producing cell was a nonadherent Fc receptor-positive lymphocyte.

Studies on the effects of Type II interferon on natural killing (NK) and antibody-dependent cell-mediated cytotoxicity (ADCC) suggest that both NK and ADCC are augmented by Type II IF treatment.

381. BLADDER CANCER - IMMUNOLOGY, IMMUNOTHERAPY AND VIROLOGY

Fahey, J. L., Brosman, S. A., Saxon, A., Dorey, F., Spina, C., Arenson, E., University of California, Los Angeles Campus, School of Medicine, Dept. of Microbiology & Immunology, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

Immunologic parameters and tumor recurrence were evaluated in a randomized group of 65 patients treated with oral levamisole or placebo and followed up to two years. There has been no difference in tumor recurrence between the levamisole and placebo groups. Monocyte motility and lymphocyte function (proliferative response to PHA) were stimulated for several hours immediately following the oral administration of levamisole. There were no long-term differences between the levamisole treated and untreated patients regarding skin test response, numbers of lymphocyte subpopulations or PHA response.

T lymphocyte function, specifically proliferative response to PHA, was shown to be depressed by increasing amounts of transitional cell carcinoma. Further assessment of patients with invasive or metastatic disease will determine if additional impairment of proliferative response is caused by adherent (monocyte) cell activity.

Assessments are planned of a) T cell regulatory functions (e.g., T-help and T-suppression of pokeweed mitogen (PWM) stimulation of immunoglobulin synthesis), b) B cell function (immunoglobulin synthesis) and c) spontaneous killing (SK) function, a property of Fc receptor cells, presumably non-T cells. Patients to be evaluated will include those who have 1) no evident cancer one year after therapy, 2) superficial bladder cancer, 3) invasive and metastatic bladder cancer without radiotherapy for previous 12 months, and 4) those who have undergone radiotherapy within the past 3 months, as well as appropriate controls.

BIBLIOGRAPHIC REFERENCES: Elhilai, M., Brosman, S., Vescera, C., Paul, J. and Fahey, J.L. The effects of treatment on delayed cutaneous hypersensitivity responses (DNCB, Cro oil; and recall antigen) in patients with genitourinary cancer. Cancer 41(5):1765-1770, 1978. Portaro, J.K., Zighelboim, J. and Fahey, J.L. Individual levels of T lymphocytes and Fc receptor cells in the normal population. J. Clin. and Lab. Immuno. 1:83-86, 1978.

382. DETECTION AND ISOLATION OF HUMAN BLADDER ANTIGENS

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Human bladder tissue removed at surgery will be heterotransplanted subcutaneously into nude mice (NIH Swiss and BALB/c) and allowed to grow in that in vivo system for short periods. The human tumor cells will grow as solid tumors and retain both genetic and cell surface immunochemical characteristics which were present in the human host. Tumors will increase in mass 20-30-fold so that the isolation and identification of tumor-associated antigens from the tumor cell membranes can be accomplished. The extracted membrane proteins will be separated and chemically characterized by isoelectric focusing and polyacrylamide gel electrophoresis (PAGE). Immunological identification of separated proteins will be by migration of the acrylamide-separated proteins into agarose containing antihuman bladder sera and by radioimmunoassay (RIA) against heterologous antisera. Sera from patients with established bladder carcinoma will be tested for humoral responses to tumor-associated antigens and will be assessed both by cytotoxicity assays using short-term cultures of tumor cells removed from mice and by RIA analyses. Such studies should lead to the isolation of antigens which would thus be clinically useful in developing assays for early diagnosis of human bladder cancer. The system should provide an understanding of the relationships between tumor growth and immune response.

BIBLIOGRAPHIC REFERENCES: Sam D. Graham, Jr., Don D. Mickey and David F. Paulson. Detection of Metastatic Tumors in Nude Mice: Brief Communication. J.N.C.I. 60:715, 1978.

383. CHARACTERIZATION OF ORGAN-SPECIFIC DIFFERENTIATION ANTIGENS OF THE BLADDER

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Antisera have been raised to membrane and cytosol fractions of normal calf bladder epithelium (ICRF Scientific Report 1978 - report 158). After prolonged immunizations the antisera are cross-species reactive, and after appropriate absorbtions, can be rendered specific for urothelium. By immunofluorescence, maximal staining of normal mouse urothelium is seen in the terminally differentiated luminal cells, localizing predominantly in the asymmetric luminal membrane. The antigen is retained by cell lines established from human bladder carcinomas, and in in vitro transformed mouse-bladder cells. Preliminary analysis of immunoprecipitates by SDS-PAGE indicates that the expression of antigen varies in different cell lines. Work is in progress to

affinity-purify the antibodies, with the eventual aim of a more detailed analysis of expression of antigen during transformation, and also in order to develop a radioassay for the estimation of antigen in clinical samples.

384. IMMUNOCHEMICAL ANALYSIS OF EPITHELIAL CELLS DURING IN VITRO TRANSFORMATION

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Mouse bladder and salivary gland cells have been transformed in vitro to give rise to pre-malignant and eventually tumorigenic cell lines (ICRF Scientific Report 1977 - reports 122, 126). These cell lines can be analyzed by single and two-dimensional PAGE. Preliminary data suggest loss and alteration of some proteins after transformation. Antibodies will be raised to individual gel bands of potential interest to characterize the changes associated with transformation.

385. IMMUNOLOGY OF BLADDER TUMORS

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We have developed a modified version of the original microcytotoxicity test, which is rapid and totally objective (counting of cells being done electronically with an image analyzer), an antibody binding assay based on the use of radioiodinated protein A, and a modified radioimmunoprecipitation test. We have used these assays with mouse sarcomas (as models) to characterize immune responses to bladder tumors in mice and plan to extend this to rats and human patients. Using the in vivo rat bladder tumor model, we are investigating the suppressor and/or blocking factors in transplanted and primary tumors.

We have been able to adopt the Milstein hybridoma technique to raise monoclonal antibodies to mouse sarcomas, and recently also to antigens associated with mouse bladder carcinomas and a human melanoma line. We have also been able to establish several lines of typical mouse bladder carcinoma cells, which grow well in culture. This has made it possible to vastly expand our planned experiments, trying to find the specificity, and the chemical nature, of antigens associated with bladder carcinomas in mice and man. Monoclonal antibodies have been raised to such antigens (using heteroimmunization procedures in the experiments with human material), and these antibodies used to make immunoadsorbents for purifying the tumor antigens.

386. IMMUNOLOGIC INVESTIGATION OF HUMAN BLADDER AND KIDNEY CANCER

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The investigation of hybridoma anti-tumor antibodies as reagents for cytotoxicity and tumor localization now confirms that the anti-teratoma hybridoma antibody is capable of localizing teratocarcinoma in the murine host. Enzymatic modification of the antibody decreases the non-specific uptake by non-tumor organs and increases the excretion of tumor unbound antibodies. These developments indicate that the application for detection of tumors in humans may be warranted since the enzyme modified antibody would reduce irradiation to the host and the studies in vitro indicate that the murine anti-tumor antibody reacts against human teratocarcinoma.

Studies designed to estimate the risks to human tumor patients by use of these radio-labeled anti-tumor antibodies are under way in preparation for requesting permission for trials in patients with teratocarcinoma.

387. CELLULAR IMMUNE RESPONSE MECHANISMS IN BLADDER CANCER

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We have used the carcinogen N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide (FANFT) to induce bladder cancer in rats in order to study the cellular immune response during tumor development. Expression of both natural and antibody-dependent lymphocyte-mediated cytotoxicity was observed to decrease early in tumor development, even though lymphocyte populations appeared unchanged and blastogenesis in mixed lymphocyte/tumor cell culture persisted. In concomitant studies, interferon (IF) stimulated lymphocyte cytotoxicity and prostaglandin E2 (PGE2) inhibited cytotoxicity. Since bladder tumor cells in response to exposure to lymphocytes and macrophages were found to produce significant amounts of PGE2 in vitro, and macrophages have been shown to produce both IF and PGE2, it was felt that the effect of these substances might be important in lymphocyte/macrophage-tumor cell interactions and in the ability of the host to respond to tumor development.

The major objectives of this investigation, therefore, are to continue characterization of the cellular immune response during bladder cancer development, to study conditions that determine production of IF and PGE2 during lymphocyte/macrophage-tumor cell interactions, and to assess effects of these substances in the manipulation of the cellular immune response and tumor development in vitro and in vivo. Lymphocyte cytotoxicity would be assessed during tumor development using Chromium 51 release assays. Interactions with macrophages, and the possible role of IF, as determined by viral inhibition assays, and PGE2, as determined by radioimmunoassays, would be studied in vitro, with subsequent application of in vitro interactions in attempts to modulate the cellular immune response and tumor development in vivo. Ultimately, results of in vitro and in vivo studies of the role of cell products (IF, PGE2) in the cellular immune response to tumor development might be applicable clinically in the inhibition of bladder cancer development in man.

VI. BROAD STUDIES AND COOPERATIVE GROUPS

A. BLADDER CANCER

388. EVALUATION AND TREATMENT OF BLADDER CANCER PATIENTS

Wajsman, Z., Beckley, S., Johnson, R. J., Englander, C. L., Gamarra, M., Higby, D., Pontes, E., Roswell Park Memorial Inst., Dept. of Urology, *666 Elm St., Buffalo, New York*, 14263, United States of America

The objectives of the collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized, and analyzed in a central statistical office.

The following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise. Studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma. The effects of radiation therapy and chemotherapy on localized bladder cancer is studied as well. The research includes also the study of chromosomal changes in bladder tumors, the cytological evaluation of bladder cancer and lymph-node aspiration biopsies of patients with bladder cancer.

BIBLIOGRAPHIC REFERENCES: Viewpoints of the Current Treatment of Bladder tumors. Wajsman, Z., Beckley, S., and Murphy, G.P.: Current Surgery: Vol 37(1):1-7, January/Feb. 1980.

389. EVALUATION AND TREATMENT OF BLADDER CANCER PATIENTS

Loening, A. A., Hawtrey, C. E., Bonney, W. W., Fallon, B., Narayana, A. S., Gerber, W. L., Culp, D. A., Penick, G. D., Corder, M. P., Latourette, H. B., Yoder, L., University of Iowa, School of Medicine, Dept. of Urology, *Jessup Hall, Iowa City, Iowa*, 52240, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The

studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, follow-up of patients entered into the following protocols is continuing: surveillance of all patients admitted with bladder carcinomas; the study of multiple mucosal biopsies from patients with frank tumor and/or positive cytology; evaluation of different forms of intravesical therapy, invasive carcinoma; radiotherapy alone and preoperative radiotherapy followed by cystectomy. The following protocols have been initiated: studies of systemic chemotherapy in patients with metastatic bladder carcinoma (Protocol 5); studies of adjuvant systemic chemotherapy in association with definitive therapy of invasive bladder carcinoma (Protocol 7); and studies of intervention (secondary prevention) in patients with completely resected low-stage lesions (Protocol 6).

BIBLIOGRAPHIC REFERENCES: Loening, S., Narayana, A., Yoder, L., Slymen, D., Weinstein, S., Penick, G. and Culp, D.A.: Factors influencing recurrence rate of patients with bladder cancer. J. Urol., 123:1, 29-31, 1980. Loening, S., Narayana, A., Yoder, L., Slymen, D., Penick, G. Culp, D.A.: Analysis of bladder tumor recurrence in 178 patients. Urol., 16:2, 137-141, Aug, '80.

390. EVALUATION AND MANAGEMENT OF BLADDER CANCER PATIENTS

Prout, G. R., Harvard University, Boston Campus, Massachusetts General Hospital, *Fruit St., Boston, Massachusetts*, 02114, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central pathology laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material. A central statistical office is responsible for data collection, organization and analyses. In each participating institution, the following protocols are being studied: assessment and characterization of patients; their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma; and studies of combined radiotherapy and chemotherapy for invasive bladder carcinoma in inoperable patients.

391. EVALUATION-MANAGEMENT OF BLADDER CANCER PATIENTS

Cutler, S. J., Georgetown University, School of Medicine, Dept. of Community & Family Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

392. EVALUATION AND MANAGEMENT OF BLADDER CANCER PATIENTS

Prout, G. R., Massachusetts General Hospital, Urological Service, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

393. EVALUATION AND MANAGEMENT OF BLADDER CANCER PATIENTS

Soloway, M. S., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Urology, *62 S. Dunlap St., Memphis, Tennessee*, 38103, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

394. MANAGEMENT OF PATIENTS WITH BLADDER CANCER

Pearse, H. D., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon*, 97201, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

395. SURVEILLANCE OF PATIENTS WITH PRIMARY BLADDER NEOPLASMS

Soloway, M. S., Jordan, W. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

The National Bladder Cancer Project plans to continue to monitor patients who enter the hospital with newly diagnosed carcinoma of the urinary bladder. The intent will be to learn more of the natural history of the disease and particularly of the various stages and grades of the initial neoplasms. This study had started approximately 4 years ago but has been interrupted for a year and now will be resumed. Cytologic evaluation as well as histologic evaluation will be critical.

396. EVALUATION AND MANAGEMENT OF BLADDER CANCER

Schmidt, J. D., University of California, San Diego Campus, School of Medicine, Dept. of Surgery, *P.O. Box 109, La Jolla, California*, 92093, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, the following protocols are being studied: Assessment and characterization of patients, their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of chemical intervention (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma.

397. EVALUATION AND MANAGEMENT OF BLADDER CARCINOMA

Kovatz, W. W., Virginia Commonwealth University, Medical College of Virginia, Dept. of Surgery, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central pathology laboratory is responsible for the uniform collection, classification and analysis of pathologic and cytologic material. A central statistical office is responsible for data collection, organization and analysis. In each participating institution, the following protocols are being studied: Assessment and characterization of patients; their neoplasms and the fields from which the neoplasms arise; studies of systemic chemotherapy in patients with metastatic bladder carcinoma; studies of systemic chemotherapy as adjuvant to definitive therapy of invasive bladder carcinoma; and studies of combined radiotherapy and chemotherapy for invasive bladder carcinoma in inoperable patients.

398. EVALUATION AND MANAGEMENT OF BLADDER CARCINOMA

Brannens, G. E., Gibbons, R. P., Correa, R. J., Wheelis, R. F., Hafermann, M. D., Einstein, A. B., Virginia Mason Research Center, *1000 Seneca St., Seattle, Washington*, 98101, United States of America

The objective of this collaborative clinical research effort is to define improved methods of treatment for bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the collection, classification and analysis of pathologic and cytologic material. All data are collected, organized and analyzed in a central statistical office. In each participating institution, the following areas are being studied; assessment and characterization of systemic chemotherapy in patients with metastatic bladder carcinoma; the role of topical chemotherapy (prevention of recurrence) in patients with completely resected low-stage bladder lesions; and advantages of systemic chemotherapy as adjuvant to radiation therapy and cystectomy to localized invasive bladder cancer.

BIBLIOGRAPHIC REFERENCES: In Vitro Immune Parameters in Relation to Clinical Course in Transitional Cell Carcinoma. K.B. Cummings, Y. Kodera, M.A. Bean. Natl. Cancer Inst. Monogr. 49, 1978.

399. NATIONAL BLADDER CANCER PROJECT

Baker, L. H., Pierce, J. M., Al Sarraf, M., Drelichman, A., Wayne State University, School of Medicine, Dept. of Oncology, *1014 Rivard, Detroit, Michigan*, 48207, United States of America

The major objective of this program is to identify active anti-cancer agents which will prolong useful survival of patients with disseminated bladder cancer. The program shall be multi-institutional and multi-disciplinary. Patients shall be treated in accordance with agreed upon clinical trials research protocol(s). All institutional participants are familiar with this clinical trials process and have established records of successful collaborative efforts.

400. NATIONAL BLADDER CANCER COLLABORATIVE GROUP A

Flanagan, M. J., Rush University, School of Medicine, Dept. of Urology, *1725 W. Harrison St., Chicago, Illinois*, 60612, United States of America

The objective of this collaborative clinical research effort is to improve the care of patients with bladder carcinoma through studies of different aspects of clinical management. The studies are carried out in several institutions simultaneously according to well-designed protocols. A central laboratory is responsible for the uniform collection, classification, and analysis of pathologic and cytologic material and all data are being collected, organized and analyzed in a central statistical office. In each participating institution, follow-up of patients entered into the following protocols is continuing: Surveillance of all patients admitted with bladder carcinoma; the study of multiple mucosal biopsies from patients with frank tumor and/or positive cytology; evaluation of different forms of intravesical therapy; invasive carcinoma, radiotherapy alone and pre-operative radiotherapy following with cystectomy. The following protocols have been initiated: Studies of systemic chemotherapy in patients with metastatic bladder carcinoma (Protocol V); Studies of adjuvant systemic chemotherapy in association with definitive therapy of invasive bladder carcinoma; (Protocol VII); and studies of intervention (secondary intervention) in patients with completely resected low-stage lesions (Protocol VI).

401. NATIONAL BLADDER CANCER CO-OP GROUP A STUDY

Cox, C. E., Jordan, W. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

The National Bladder Collaborative Group A is a multi-institutional group designed to determine the efficacy of various therapeutic decisions in bladder cancer. An important aspect of the study has been the prognostic value as well as incidence of random selected site biopsies. This study is near completion and indicates a high incidence of epithelial hyperplasia, atypia, or carcinoma in situ as well as occasional incidences of carcinoma in these biopsy sites. The patients exhibiting one of these abnormalities in a biopsy have a greater likelihood of subsequent bladder tumor recurrence. The second part of the study has determined that prophylactic thio-TEPA inhibits the subsequent recurrence rate of superficial tumors. A number of current studies are being planned including adjuvant chemotherapy with cis-platinum as well as definitive therapy of metastatic bladder cancer by the use of cis-platinum or cis-platinum plus Cytoxan (cyclophosphamide).

402. MANAGEMENT OF THE NATIONAL BLADDER CANCER PROJECT

Friedell, G. H., Greenfield, R. E., Hilgar, A. G., St. Vincent Hospital, *25 Winthrop St., Worcester, Massachusetts*, 01604, United States of America

This research grant application proposes the continuation of a Headquarters at St. Vincent Hospital in Worcester, Massachusetts, for the management of a national research program on bladder cancer. The research performed in this program will be carried on in various institutions across the country and, where a need is indicated, in selected institutions in foreign countries. Although this application is concerned specifically with the development and operation of the Headquarters of the project, an outline of the proposed national research plan is also presented so that the functions of the Headquarters staff can be more readily understood.

Studies are supported which seek 1) to identify carcinogenic factors and develop methods for minimizing their effect, 2) to improve detection methods and identify new high risk populations, 3) to increase understanding of the pathogenesis and carcinogenesis processes and find methods for interferring with these processes, 4) to develop improved methods of diagnoses in order to identify those patients most suitable for a specific available treatment regimen, and 5) to find better methods of treating the disease.

Scientific direction of the project will come from the Program Director and the Bladder Cancer Subcommittee of the Bladder and Prostatic Cancer Review Committee, who will be responsible for developing the program and reviewing the mul-

tiple scientific aspects of its operation on a continuing basis. All research activities will be supported by research grants, with the Program Director and his Headquarters Staff having administrative responsibility for the review and initial processing of all grant applications. Management guidelines for this function have been developed and are in use. Any modifications in procedures which have been made are discussed in this application.

BIBLIOGRAPHIC REFERENCES: Friedell, Gilbert H., Greenfield, Robert E. and Hilgar, Arthur G., Guest Editors: Carcinoma of the Urinary Bladder. Seminars in Oncology, June 1979, in press. Ellwein, Leon B., Friedell, Gilbert H., Greenfield, Robert E. and Hilgar, Arthur G.: Disease Process Modeling as a Tool for Planning. Seminars in Oncology, June 1979, in press.

403. SOUTHEAST CANCER STUDY GROUP

Chang Wai Ling, B. K., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Division of Hematology & Oncology, *Wrightsboro Rd., Augusta, Georgia*, 30904, United States of America

OBJECTIVES: 1) To improve cancer therapy through scientific testing and evaluation of innovative and rational treatment methods. 2) To study sufficient numbers of appropriately selected patients to answer important clinical problems within a reasonable length of time. 3) To stimulate original scientific thought through the collaborative efforts of qualified investigators and clinicians representing a number of institutions.

RESEARCH PLAN: Active protocols at the Augusta VAMC include those for the treatment of small cell carcinoma of the lung, breast cancer, prostatic cancer, testicular cancer, bladder cancer, sarcoma, hepatoma, bile duct and gall bladder cancer, melanoma, metastatic thyroid cancer, acute leukemia, multiple myeloma and Hodgkin's disease and non-Hodgkin's lymphoma.

METHODOLOGY: All patients require a careful diagnostic workup, including pathologic examination, often confirmed in reference laboratories. Patients on Phase III protocols are randomized according to standard techniques. Phase I and II protocols are non-randomized. Treatment is carried out according to protocol guidelines, and all patients receive careful clinical follow-up and documentation of their disease course. Response to therapy, duration of response, toxicity, and survival are the end points commonly used to evaluate protocols. Data is analyzed and computerized by the Central Office of the SEG (University of Alabama) by means of periodic progress reports that are submitted on each patient entered onto protocol study.

RESULTS: For most of the active SEG studies, it is too early to evaluate the results. The active protocols are continuously being evaluated and, whenever necessary, revised. Five patients from the Augusta VA Medical Center have been entered onto protocol in the past year. All patients must meet very rigorous criteria in order to be eligible for protocol study. It is too early to report on the results of treatment in these patients.

404. SURVEILLANCE OF PATIENTS WITH PRIMARY BLADDER CANCER - INVESTIGATIONS OF NON-CANCEROUS VESICLE EPITHELIUM (ABBREV)

Koontz, W. W., Smith, M. J., Texter, J. H., Hackler, R. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1201 Broad Rock Rd., Richmond, Virginia*, 23249, United States of America

Two hundred and sixty-four patients have been contributed to the Study by the Medical College of Virginia and McGuire Veterans Administration Hospital in collaboration with the National Bladder Cancer Project Collaborative Group A. Eighty-four of these patients are dead, 86 continuing Regular Follow-up, 6 Vital Status only, 6 Registration A only, 74 in Registration B only and only 8 Lost to Follow-Up.

Fifty-four patients have been admitted to this Study since the last Progress Report of April 12, 1979. This confirms the steady admission of patients via the MCV/McGuire V.A. Complex of 35 - 50 per year with an increase in the last year. Since the reinstitution of the 1A Surveillance Protocol in May, 1980, 9 patients have been admitted.

The Medical College of Virginia and McGuire V.A. Complex have continued to participate in the Collaborative Study which has brought together a multidisciplinary group of urologists, pathologists, cytologists, radiation therapists, medical oncologists, and statisticians in making an effort to study the management of carcinoma of the urinary bladder. Protocols have been designed and implemented to assess systemic treatment of early, invasive, and metastatic disease.

405. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Canellos, G. P., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III Studies in Patients with Disseminated Solid Tumors. The tumors to be included in these studies shall be limited to the following: Large bowel cancer, bronchogenic cancer, malignant lymphoma, head and neck cancer, endometrial cancer, ovarian cancer, bladder cancer, soft tissue cancer, breast cancer, prostate cancer, bone sarcoma. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one tumor type group.

406. STUDIES OF PATIENTS WITH SOLID DISSEMINATED TUMORS

Burchenal, J. H., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III studies in patients with solid disseminated tumors. The tumors to be included in these studies shall be limited to the following; lung carcinoma; ovarian carcinoma; cervical carcinoma; head and neck cacinoma; prostatic carcinoma; bladder carcinoma; and melanomas and sarcomas of soft tissue. A minimum of 400 patients shall be included in these studies with no less than 25 patients from any one tumor type. All patients shall be treated intensively with chemotherapy either alone or in combination with other drugs, radiotherapy, immunotherapy or surgery in protocols to be agreed upon by the Project Officer and Principal Investigator. Protocols will include Phase II testing of new investigational drugs, Phase II testing of standard antitumor drugs not previously tested against the particular tumor type, and Phase III trials to determine the definitive activity of the above regimens.

407. STATISTICAL CENTER FOR NATIONAL BLADDER CANCER CONFERENCE

Mike, V., Braun, D. W., Yagoda, A., Sloan Kettering Inst. for Cancer Research, Biostatistics Laboratory, *410 E. 68th St., New York, New York*, 10021, United States of America

The National Bladder Cancer Project Confederation is a group of institutions collaborating in cooperative clinical trials to evaluate the clinical effectiveness of chemotherapeutic agents in the treatment of patients with urothelial cancer. This proposal requests continued funding for the Biostatistics Laboratory of Memorial Sloan-Kettering Cancer Center to serve as the Statistical Center for this project.

408. CONTROL OF BLADDER CANCER

Troll, W., New York University, School of Medicine, Dept. of Environmental Medicine, *550 1st Ave., New York, New York*, 10016, United States of America

This is part of a broader project. A summary of this subproject is not available.

409. BLADDER AND LUNG CANCER (HUMAN)

Kellerman, G., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

410. BLADDER CARCINOMA (CHILDREN)

Bing, D. H., Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

411. BLADDER CANCER

Yagoda, A., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. WILMS' TUMOR

412. NATIONAL SURVEY OF CHILDHOOD CANCERS

Kinnier Wilson, L. M., Stewart, A. M., Draper, G., Doll, R., Marie Curie Memorial Foundation, Research Dept., Epidemiology Unit, *The Chart, Oxted, Surrey RH8 0TL, England, United Kingdom*

This long-standing retrospective survey was orginally started in Oxford by Dr. A. Stewart in 1953 to study the aetiology of childhood cancers. It consists of interviews with the parents of children under 16 dying of cancer or leukemia in the United Kingdom and with parents of control children matched for age, sex and district; antenatal information is confirmed by application to clinics and doctors, and the case child's medical history is followed up through general practitioner and hospital notes. Surviving children have similarly been interviewed and followed up since 1962 by means of the regional cancer registries. In the past extensive studies have been made of the relation of obstetric low-level radiation to the increased risk of the child later developing neoplasia. The effect of viral diseases during pregnancy has also been found to increase the risk, but less convincingly. Present projects include: 1. A study of the effects of the use of ultrasound and of drug therapy during pregnancy, and of the possible relationship of these agents in the aetiology of childhood cancers. 2. A study of congenital defects found in children who later develop cancer or leukemia, and congenital defects in their siblings, together with a similar study of defects in matched control children and their siblings. 3. A study of all cases of Wilms' tumor, surviving and dead, whose diagnosis and initial treatment occurred in 1969-1973 to assess the difference in prognosis between those who were included in the M.R.C. Trial and those outside. This study is being done in collaboration with the C.C.R.G. in Oxford. 4. A study of 95 second primary tumors occurring in children after cure of their initial cancer is being undertaken with special attention to the effect of radiation and genetics.

413. CANCER CENTER SUPPORT GRANT (SPECIALIZED)

Camitta, B. M., Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin*, 53233, United States of America

The diagnosis of cancer in a child is no longer synonymous with death. However, cancer is still the leading cause of death from disease in American children over one year of age. In addition, most of the major advances in treatment were made prior to 1970 and the dismal prognoses of some tumors (T cell leukemia, disseminated neuroblastoma) remain unchanged. Even in therapy-responsive tumors such as common cell ALL, lymphomas and Wilms' tumor, 20-50% of children relapse. Clearly there is a need for more fundamental knowledge about the origin, biologic properties, subtypes, and reasons for varying responsiveness to therapy of different childhood tumors.

The Midwest Children's Cancer Center is a clinical research facility, associated with research laboratories focusing on problems generated by patient care. The six general objectives of the Center are: (1) Determination of pharmacokinetics, mechanisms of action and efficacy of new anti-cancer drugs; (2) development of further understanding of the immune system in children with cancer and possible ways of utilizing it for treatment; (3) development of new anti-cancer treatments by comparative and exploratory studies; (4) assessment of infectious problems in children with cancer and ways of treating or preventing them; (5) provision of childhood cancer education for physicians, basic scientists, students, nurses, and the public; (6) collaboration with neighboring institutions, other Cancer Centers and community programs.

On a larger scale, the Cancer Center's aim is to generate awareness, interest and involvement in childhood cancer by the medical community and lay public. It also serves as a model for organization of care and research for other life threatening diseases requiring intensive long-term multidisciplinary treatment.

BIBLIOGRAPHIC REFERENCES: Pinkel, D., Hustu, H.O., Aur, R.J.A., Smith, K., Borella, L., and Simone, J.: Radiotherapy in leukemia and lymphoma of children. Cancer, 39:817, 1977. Borella, L., Sen, L., Dow, L.W., and Casper, J.T.: Cell differentiation versus tumor-related antigens in childhood acute lymphoblastic leukemia (ALL). Clinical significance of leukemia markers. Haematology and Blood Transfusion 20:77-85, 1977.

414. LATE FOLLOW-UP OF CURED WILMS' TUMOR PATIENTS

D'Angio, G. J., Children's Hospital of Philadelphia, Children's Cancer Research Center, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

The objectives of this portion of the National Wilms' Tumor Study are (1) to study the delayed adverse effects of therapy including impaired function of various organs, and oncogenesis, and (2) to seek clues as to etiology by looking for patterns of familial disease in parents and siblings with a view towards identifying possible genetic and environmental factors. At present approximately 300 long term survivors are seen regularly in follow-up, and this number will increase by about 110 children annually for the next three years.

415. CHILDHOOD CANCER REGISTRY

Draper, G. J., Kinnier Wilson, L. M., Lennox, E. L., University of Oxford, Dept. of the Regius Professor of Medicine, Childhood Cancer Research Group, *9 Keble Road, Oxford OX1 3QG, England, United Kingdom*

A registry for childhood neoplasms occurring in England, Scotland and Wales has been established with the following objectives: (1) To obtain estimates of incidence, mortality and survival rates, (2) to provide a basis for epidemiological, genetic and medical care studies, (3) to provide a service to other research workers. Registrations of cancer in children below age 15 and deaths below age 16 are reported to the Childhood Cancer Research Group by the Office of Population Censuses and Surveys, the Information Services Division of the Scottish Health Service, regional cancer registries, and clinicians. This is supplemented by clinical information derived from hospitals and general practitioner records. A classification system particularly appropriate for childhood cancer and based on the International Classification of Diseases for Oncology has been developed. Comprehensive data on incidence, mortality and survival have been analyzed and will be published by the Office of Population Censuses and Surveys. Studies currently in progress include: (1) Comparisons of survival rates for children with leukemia and Wilms' tumor included in MRC clinical trials with those for children not included, (2) the provision of treatment for children with cancer, (3) studies to determine whether there is an increased incidence of cancer in the parents of children with cancer.

C. OTHER RENAL AND UROLOGICAL SYSTEM NEOPLASMS

416. GENERAL CLINICAL RESEARCH CENTER

Grover, M. R., Porter, J. M., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon*, 97201, United States of America

The Clinical Research Center at the University of Oregon Health Sciences Center is currently conducting human research across a wide number of human disease states as well as numerous physiologic and pharmacologic observations on normal volunteers. Subjects under active investigation at the present time include: (1) solid tumor chemotherapy, (2) progesterone, prolactin and estrogen interaction and manifestations in metastatic breast carcinoma, (3) hyperlipidemia and cholesterol metabolism, (4) Raynaud's syndrome and other vasospastic diseases, (5) autoimmune diseases, (6) bronchial asthma, (7) effect of methadone on respiration, (8) investigations of new diuretic agents, (9) studies on growth hormone, (10) agammaglobulinemia, (11) hyperlipidemia of renal disease, (12) evaluation of floctafenine, (13) blood pressure control, (14) parathormone secretion in end-stage renal disease and parathyroid secretory function after parathyroidectomy, and (15) evaluation of hypersecreting pituitary tumors.

417. NEPHROMA (HUMAN)

Smalley, R. V., Temple University, School of Medicine, Dept. of Internal Medicine, *3322 Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

This is part of a broader project. A summary of this subproject is not available.

418. GENITO-URINARY TRACT (HUMAN)

Chan, R. C., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

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Westwood Building, Room 10A18
Bethesda, Maryland 20205

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If you have already submitted a description of your research to the Smithsonian Science Information Exchange (SSIE), to the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or to the Current Cancer Research Project Analysis Center (CCRESPAC) within the past eight (8) months, please do not fill out this form.

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1) FULL TITLE OF CURRENT CANCER RESEARCH PROJECT

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